

Professor Neil A. Williams

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Founder, Director of Science, KWS BioTest Ltd

Founder, Aegis (Hunter-Fleming) Pharmaceuticals Ltd

Spinning out in the UK – personal experiences and perspectives



Chronology

- 1995 First patent filing “Novel therapeutic agents...”
- 1997 First R&D spin-out (Oratol Ltd)
- 1998 Collapse of Oratol
- 1999 Second R&D spin-out (Aegis Ltd)
- 2001 Aegis merger with Hunter-Fleming Ltd
- 2003 First CRO spin-out (KWS BioTest Ltd)

The science

The Daily Mail

Tummy-bug drug in arthritis breakthrough

TWO separate scientific discoveries could bring new hope to sufferers of rheumatoid arthritis.

One team of researchers, in Dijon, is developing a promising drug extracted from the bugs which cause 'holiday diarrhea'.

Another group, at Glasgow University, has identified a naturally-occurring compound which might revolutionise the treatment of chronic inflammatory diseases, by avoiding existing steroid treatments which can have debilitating side-effects.

The advance made at Bristol University came from a bizarre source - a study of bacteria which

By JENNY HOPE Medical Correspondent

They involved, said: "We found it is composed of two bits and one of the bits - which is not toxic and doesn't cause the disease - is something which can be used to change the way our immune system goes wrong. This particular agent can potentially treat arthritis."

The new drug has produced promising results in laboratory tests, and trials on patients could start next year.

The breakthrough in Glasgow is the result of ten years' research. Dr Emily Stevenson and Dr Tony Lawrence, with the assistance of Dr David Philip from The Technical Centre, Glasgow

system reacts out of control and producing excessive inflammation.

Dr Stevenson explained: "Inflammation is part of the body's natural defence system. Infection or injury and any acute inflammatory disease, resulting in the acute and often dramatic damage of chronic inflammatory disease."

The researchers believe the compound they have identified, a peptide called thymosin beta 4, plays a role in one of the body's natural ways of signalling that defence mechanisms need to destroy bacteria and started to damage blood vessels and should be avoided.

Their pioneering study, funded by the late Glasgow businessman John Uffell, was

The kinder side of the E.coli bug

The fight against auto-immune disease could get help from an unlikely source, says Geoff Watts

As the raw material for a new way of treating rheumatoid arthritis, the poison produced by a diarrhoea-inducing bacterium does not sound too promising. Neil Williams of Bristol University's department of immunology thinks otherwise.

The bacterium itself is a variety of *E. coli*, one of the commonest causes of diarrhoea. The watery outpouring serves the organism's purposes by ensuring that its descendants are spread far and wide, and so stand a fair chance of reaching the drinking water of some other potential host.

The poison with which *E. coli* engineers intestinal mayhem is a protein comprising two chunks referred to as the A and B sub-units. "The A sub-unit is the bit that actually gets into the cells of the gut and makes them secrete water and so cause diarrhoea," explains Dr Williams. "We're working on the B sub-unit. On its own it is not toxic. The bacteria use it just to get the A sub-unit into the gut cells. B sub-units do this by binding to receptors, specialised molecules on the surfaces of the cells."

Isolated B sub-units still bind to cell receptors, says Dr Williams. But with payload to deliver, that is all they do - gut cells. "What we noticed a few years ago that if they attach not to gut cells but within the immune defence system, they actually modify the way these cells behave."

Rheumatoid arthritis is an auto-immune disease: one in which the immune defence begins to attack part of the body it is supposed to be protecting. Evolution has produced an elaborate and effective method of distinguishing self from non-self and acting accordingly. But there is, inevitably, a balance to be struck. The exercise of vigilance sufficient to destroy all bacteria, viruses and other genuine intruders must be prevented from turning into a gung-ho assault on any bit of the body itself that raises the slightest hint of suspicion.

"Auto-immune disease is a process in which that balance has gone wrong," says Dr Williams. "The immune system fails to recognise that, in the case of arthritis, components of our joints are actually part of us. It starts to see them as

Not all bad

A BUG that causes food poisoning may ease the pain of arthritis sufferers, scientists from the University of Bristol said this week. Some strains of *Escherichia coli* are notorious for causing diarrhoea. But the researchers told the British Society for Immunology's annual congress in Harrogate that the bacteria also produce a small protein that damps down the overactive immune systems that wreck the joints of arthritis patients.

Ironically, the protein is a non-poisonous part of the enterotoxin that causes so many cases of the squits. Tests in arthritic mice show it to be safe and effective. Although it has yet to be tested on people, it may also help those with related conditions such as Crohn's disease and multiple sclerosis, says Bristol researcher Neil Williams.

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confirmed their hopes.

"What we are attempting to do to these cells is not destroy them but re-educate them. We've started work with human blood samples to see that the sort of effects we are looking for do also occur in humans. We are very hopeful that the data we already have make a strong case for a clinical trial."

The protein can be administered by injection, by mouth and even by nasal spray. And if it works in rheumatoid arthritis, Dr Williams is hopeful that it might also be effective in other auto-immune conditions such as multiple sclerosis.

New Scientist

The Times, London



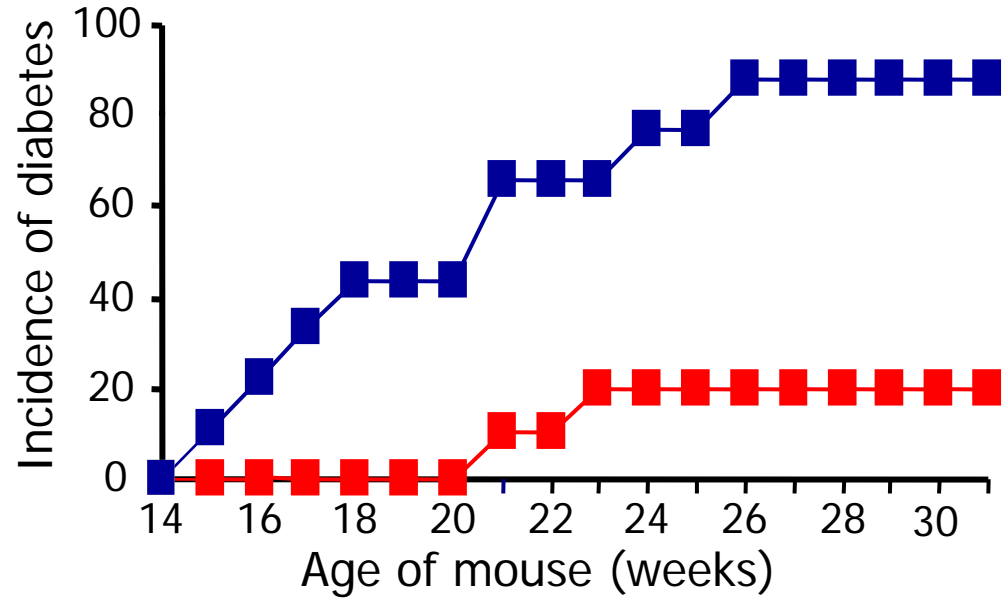
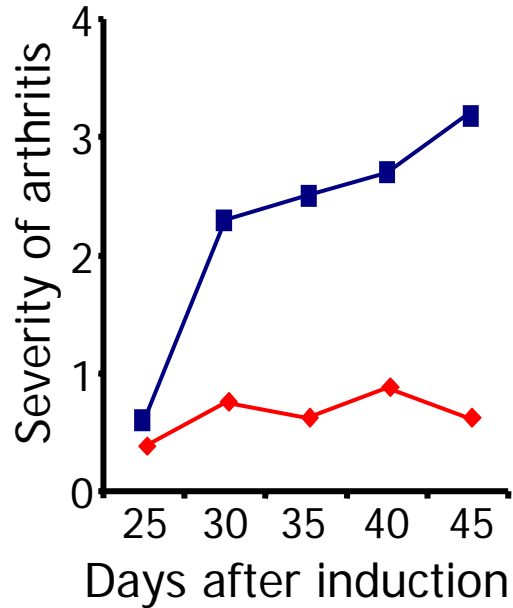
The science



- EtxB
- The non-toxic subunit of a diarrhoea causing protein produced by some *E. coli*
- A potent immune modulator

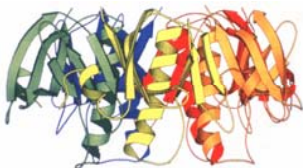
The science

■ untreated ◆ treated

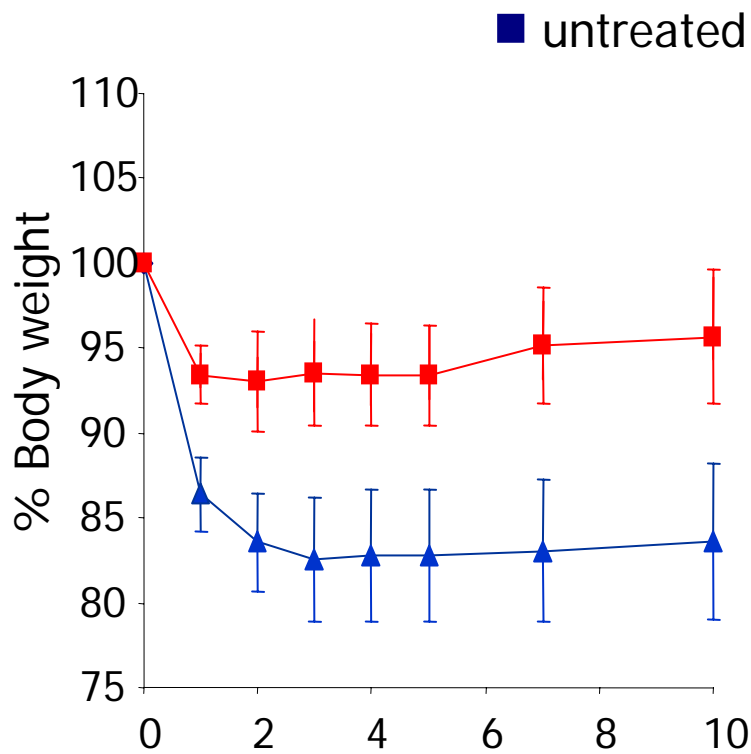


Rheumatoid arthritis?

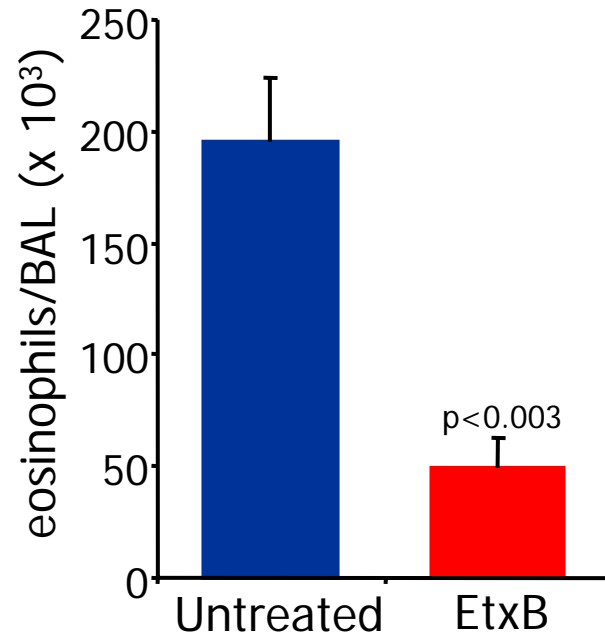
Type 1 diabetes?



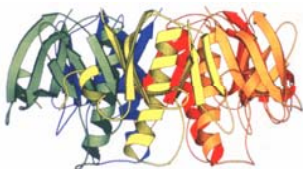
The science



Crohn's disease?



Asthma?



First attempt (1996-1997)

• The environment

- Internal funding possibilities – none
 - Pitches to pharmaceutical companies
- Patent budget – support up to PCT
 - British Biotech (evaluation agreement)
 - GSK (license offer)
- University Manpower – 1 person (IP licensing), 1 person (contracts)
 - Cortecs International Ltd (lets spin out together!)
- Cortecs and University of Bristol joint venture
- Venture Capital environment - very favourable
 - Orator Ltd
 - £10M raised from VCs 1997

First attempt (1997-1998)

- £1.2M research funding to University of Bristol
- £100K license fee
- Equity to University and Founders
- Consultancy agreements to Founders

12 months later.....

- 3 further patents
- Cortecs Ltd collapses
- Investors close Oratol Ltd!!
- **Patents revert to University**

Second attempt (1998-2000)

• The environment (Aegis Pharmaceuticals Ltd)

- Founders paying consultants help with business plan
- Patent through ESRC Business Plan Competition 2000
- Prize money finances VC visits, continued
- Mandatory Business Enterprise Centre
- Message = "very interesting, but need to spread the risk"
– dedicated IP, licensing, contracts personnel
– limited spin out experience
- Venture Capital environment - tight

Second attempt (2000-2001)

- Summer 2000 – merger discussions with Hunter-Fleming Ltd
- January 2001 – Hunter-Fleming acquires Aegis in share exchange
- Spreads the risk (Hunter-Fleming has 3 products in CNS area)
- Brings in money (Hunter-Fleming receives £4.2M from private and corporate investors)

Second attempt (2000-2001)

- Founders: 1 board position, 2 members of Scientific Advisory Board.
- Consultancy agreements to founders
- Equity stake escalates with milestone achievements (GMP manufacture, toxicology, first in man study)
- Virtual company model means £0.6M research investment into University

Second attempt – Hunter-Fleming (2001-now)

- July 2002 refunding led by M.T.I., £5m + £3.5m follow-on Q3, 2003.
- Spring/Summer 2005 – require approx. £30M to get 2 major products (EtxB + HF0220) into phase II in man
- Collaboration with big pharma (licensing/joint development) vs further VC investment??

Spinning out a CRO business in a new climate (2003-2004)

Why?

~~Inquiries from pharmaceutical and biotech companies~~

- ~~Expensive to develop, need to use expertise R&D~~
- ~~Costs too high and reliability (academics don't deliver)~~
- Grant funding of staff in University does not allow delivery

In vivo disease models

Autoimmunity

Arthritis
Multiple sclerosis
Inflammatory bowel disease
Type 1 diabetes
Autoimmune uveitis
Sjogrens syndrome
Autoimmune haemolytic anaemia

Allergy
Acute asthma

Vaccines
Adjuvant efficacy
Immunogenicity
Th1/Th2 balance
Human T cells

The environment

- Internal funding possibilities –
 - Enterprise development fund (up to £30K)
 - Sulis investment fund (up to £250K)
 - Wellcome Trust University Translation Awards (up to £250K but negotiable)
- Patent budget – limited but larger
- Manpower – Research and Enterprise Development
 - Dedicated IP, licensing, contracts teams
 - Extensive spin out experience
 - Customer care, marketing support staff
 - Network of universities sharing experience
- Venture Capital environment – very tight



KWS BioTest (2003-2004)

- Enterprise Development Fund - £18K (Aug 2003)
 - Consultant to help write business plan,
 - carry out market research,
 - Interim management provision until funding received

- Sulis investment - £200K (Sept 2004)
 - 2 x £100K tranches (50% loan. 50% equity investment (20%))
 - Second £100K if required after 12 months

The logo for KWS BioTest features the letters 'KWS' in white inside a blue oval with a yellow border, followed by the word 'BioTest' in a blue, italicized sans-serif font. A series of small blue dots forms an arc above the text.

KWS BioTest (2004-2005)

- Laboratory refurbishment
- Interim management secured
- Employment of key staff
- (marketing through collaboration deal (Nov 2004))



- Aug 2005
 - Year 2 - in profit
 - Second tranche from Sulis - delayed decision
 - Expanding offering

In vivo disease models

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Vaccines
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In vivo disease models

Autoimmunity

Arthritis
Multiple sclerosis
Inflammatory bowel disease
Type 1 diabetes
Autoimmune uveitis
Sjogrens syndrome
Autoimmune haemolytic anaemia

Infection

Bacterial thigh infection
Peritonitis
Pulmonary infection*
Herpes simplex virus-1
(ocular, dermal)

Vaccines

Adjuvant efficacy
Immunogenicity
Th1/Th2 balance
Human T cells

Inflammation

Osteoarthritis*
DTH
LPS induced cytokines

Wound healing*

Dorsal incision

Cancer

Renal carcinoma
SCID models

Allergy

Acute asthma
Chronic asthma

Looking back – Why would you spin out?

- To bring in research funding to the laboratory?
 - Maybe, but it is easier/quicker to get grants to fund research
- To get rich?
 - Maybe, but do not hold your breath (I'm still waiting!)
- To see if your ideas can actually make a difference?
 - Definitely, but balance aspirations and decide on license or spin out
- To learn lots of new skills and experiences?
 - Definitely, it has been great fun

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HUNTER  FLEMING

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