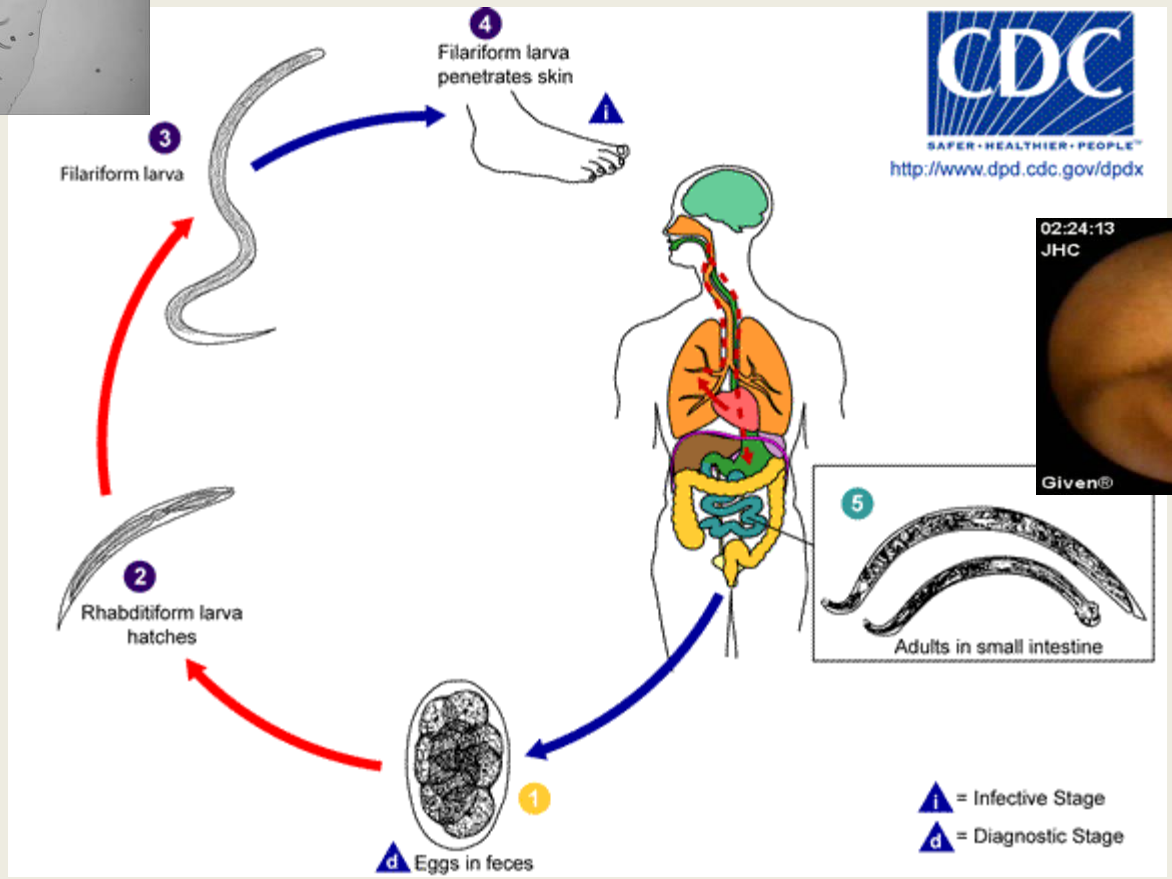
Hookworms : [1]The Living Drug
[2]Origin / [3]Manufacture / [4]Vaccines / [5] Coeliac



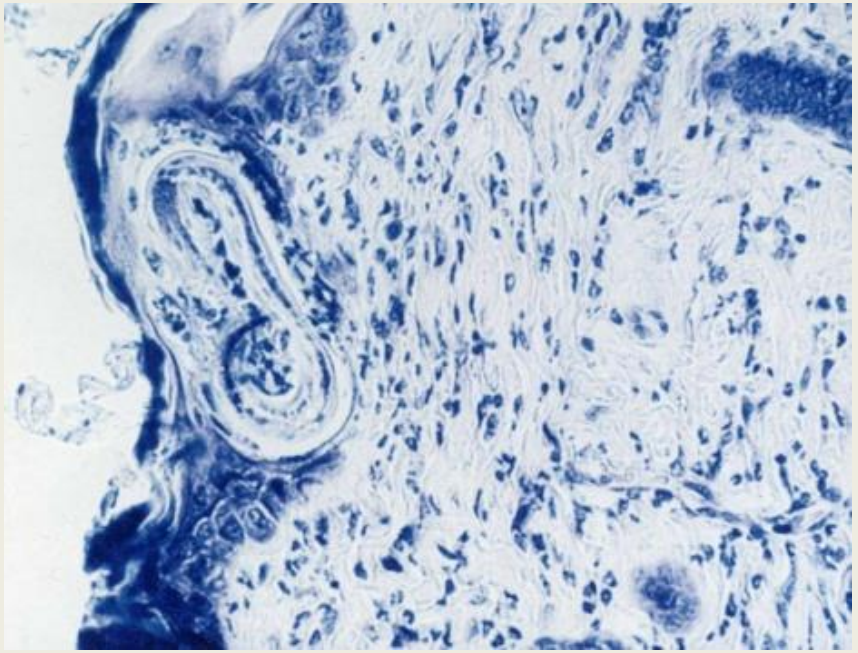
Necator americanus – the living drug

- A parasite of humans
- Easily delivered and removed
- No transmission
- Does not increase in number internally
- Long lived immune moderation by safe doses

MHRA
Regulating Medicines and Medical Devices

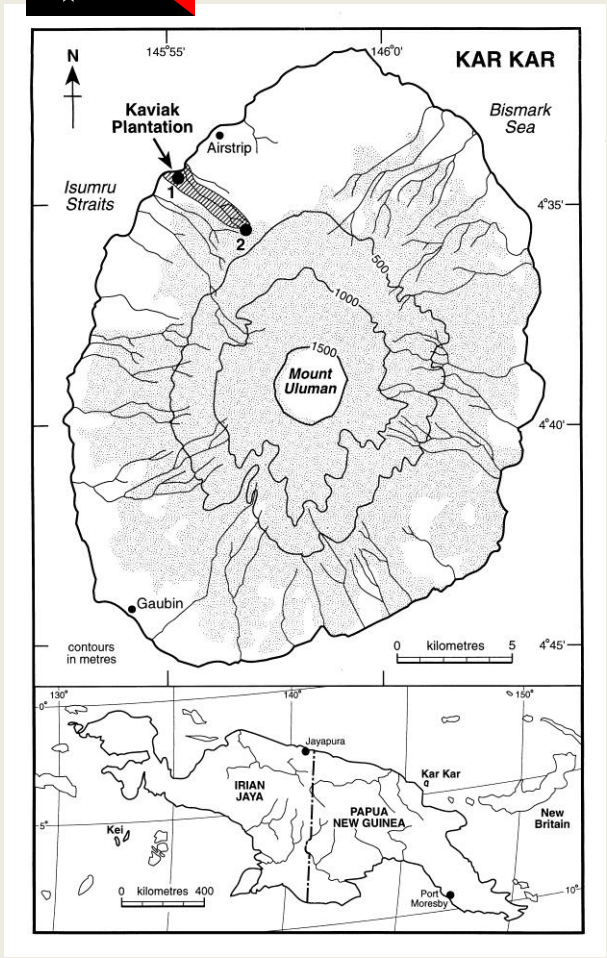
The living drug-packaged for delivery to the gut

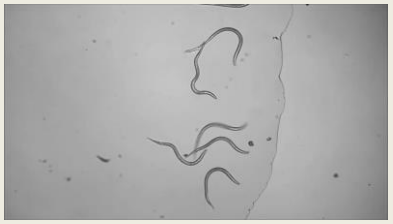
Living drug application

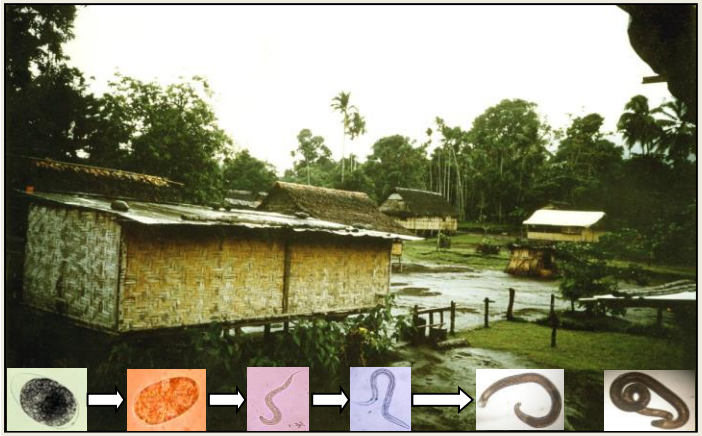


Arrival of the living drug in the gut

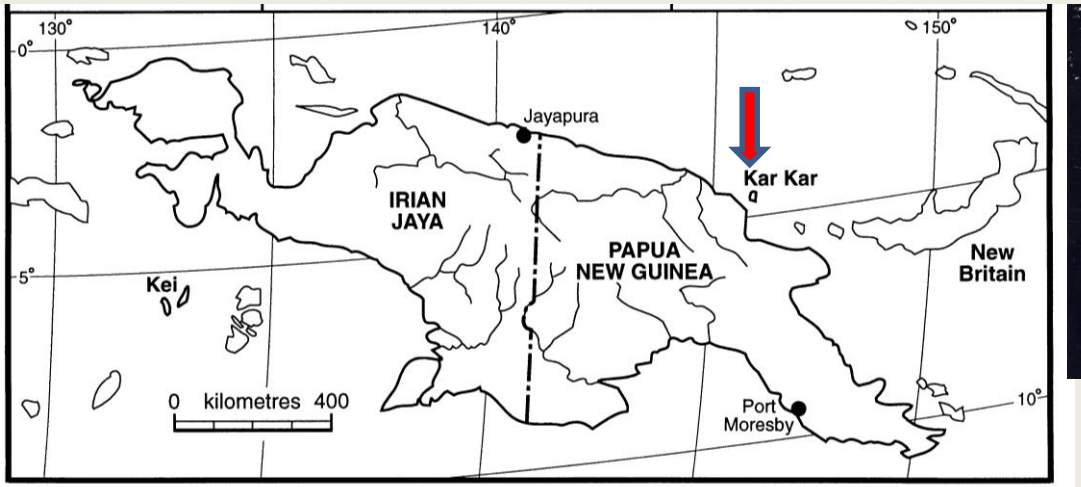
Worms originate from PNG

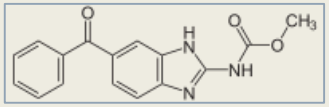


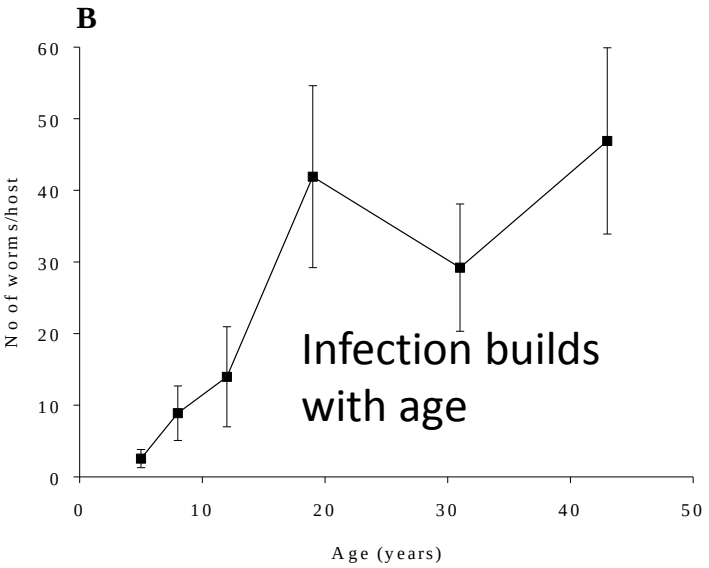


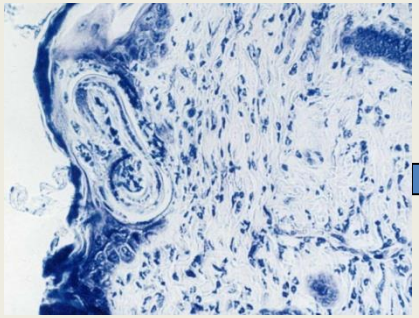


The Nottingham Isolate





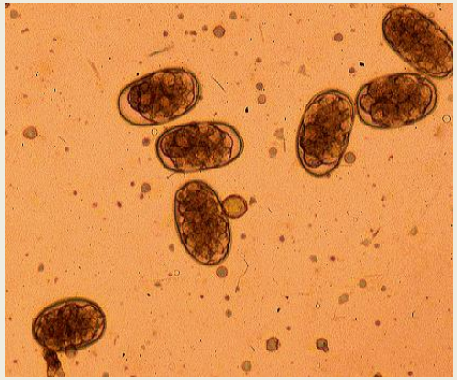




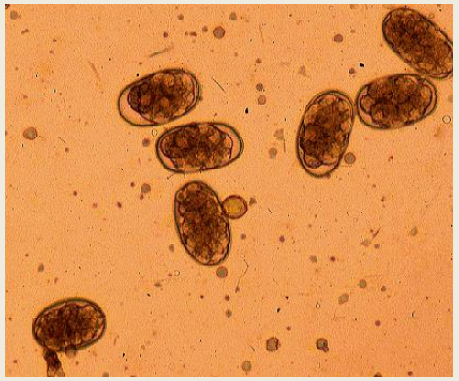
Infective L3 larva to skin

Transit lungs

Swallowed to intestine



Ova in faeces on the ground

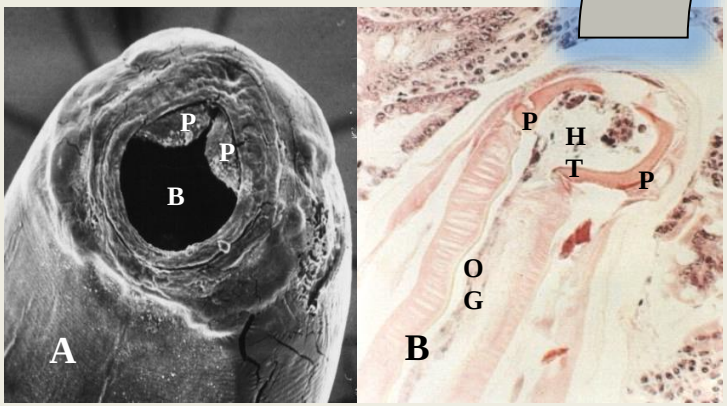


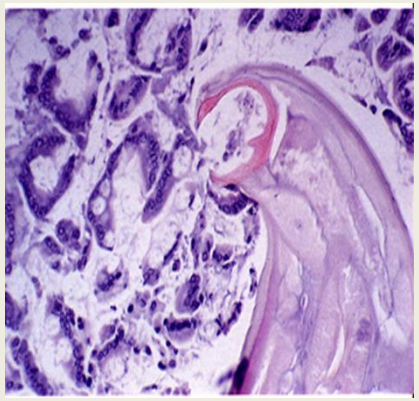
Life cycle of *Necator americanus*

Conclusions from field work

- In the tropics, hookworms are acquired regularly
- Infection builds to dangerous levels in the body
- The parasite is immune suppressive
- Vaccines are needed in the tropics
- Harness the therapeutic capacity of the worm in UK?

Biochemical mechanisms of immune suppression



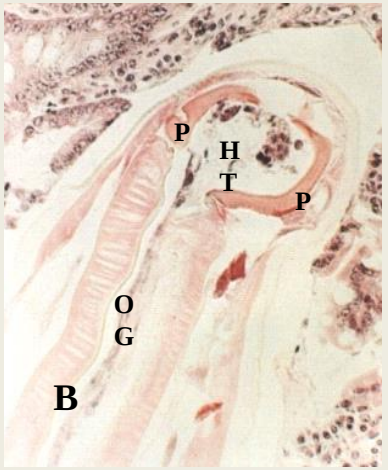


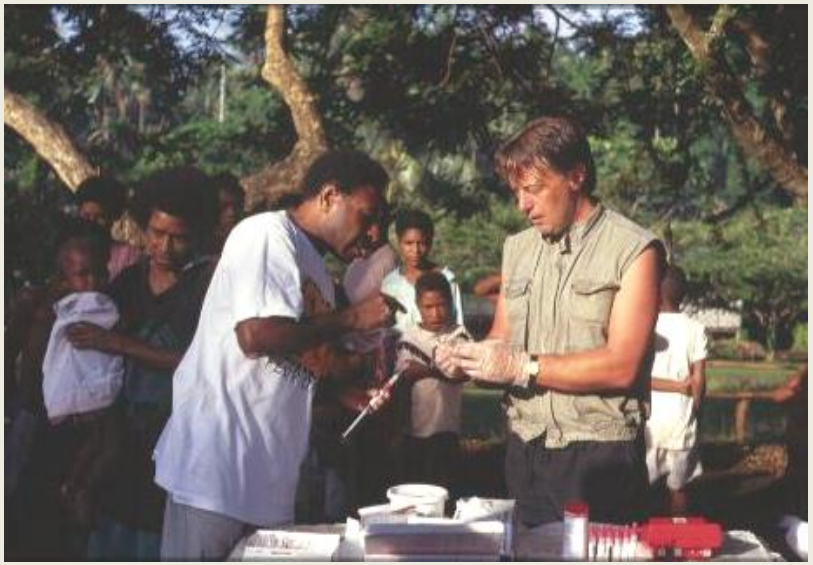
Parasite secretion (target)

Calreticulin (C1q)
GST/SOD (ROS)
Kaliseptine (T cells)
Apoptosis (T cells)
Eotaxin and IgA proteinases

As a result of this work, *Necator americanus* was harnessed for immunotherapy

- We know the parasite
- Good epidemiological and molecular data for anti-inflammatory effect
- Low dose (25 larvae)= mild or no symptoms
- Effective and safe expulsion chemotherapy
- No transmission from study participants to family and general population





Medicines and HealthCare Products Regulatory Agency (MHRA) Licence

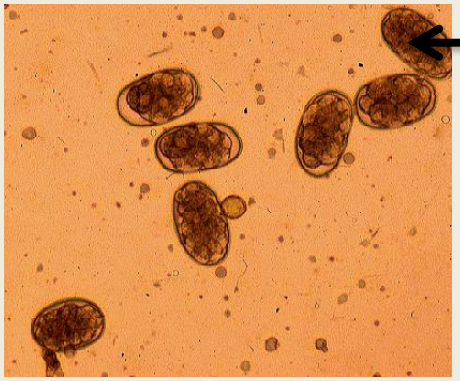
Our c GMP product

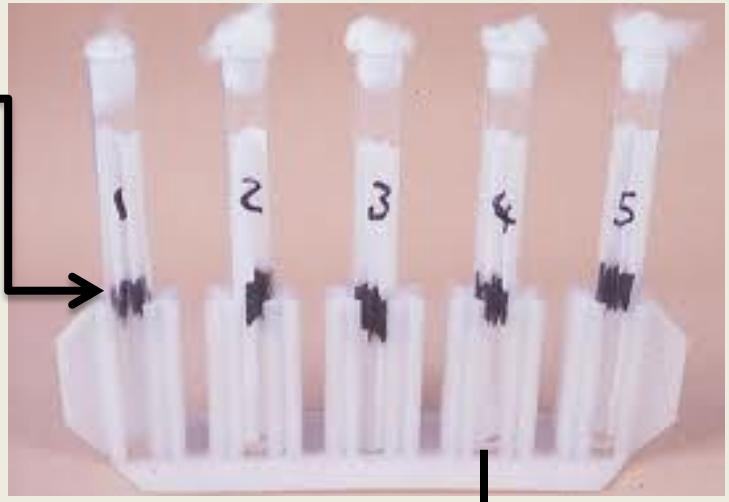
Necator americanus infective larvae - iL3

MHRA
Regulating Medicines and Medical Devices

Isolate Maintenance

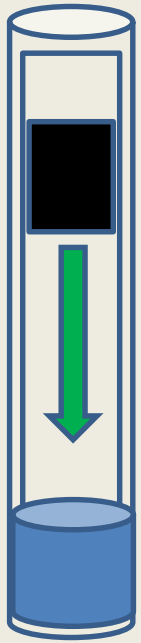
Eggs in faeces



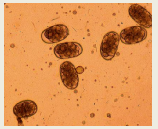


10 days

Infective larvae

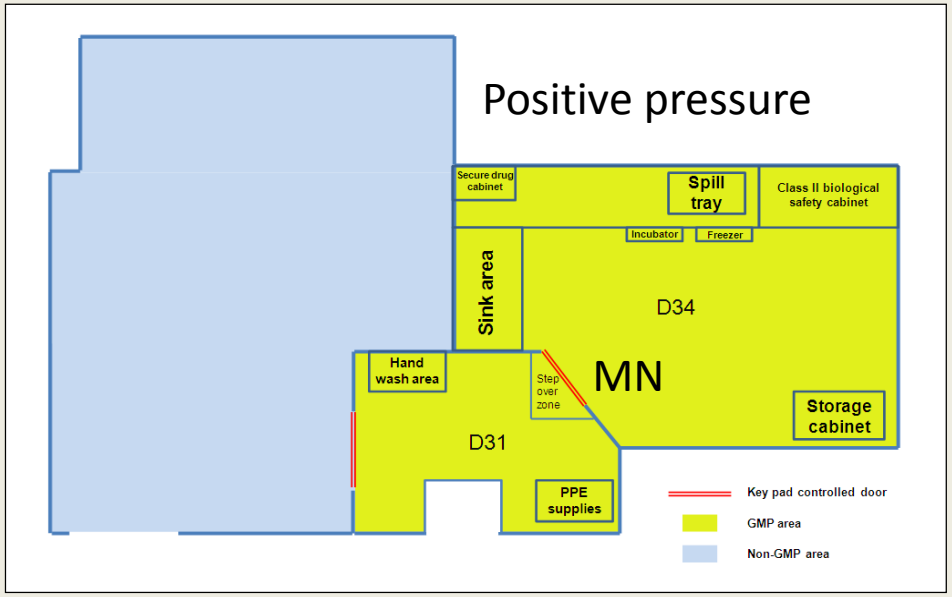


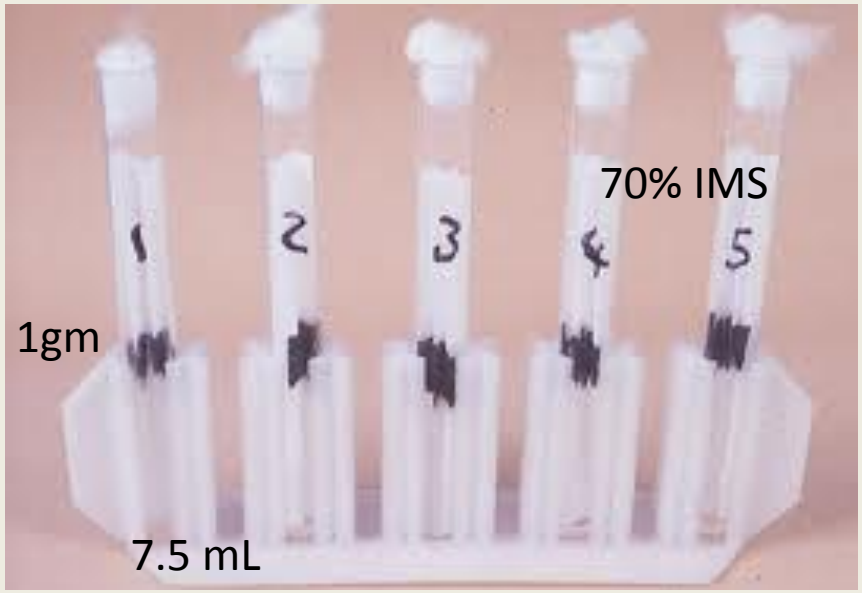
Hatch

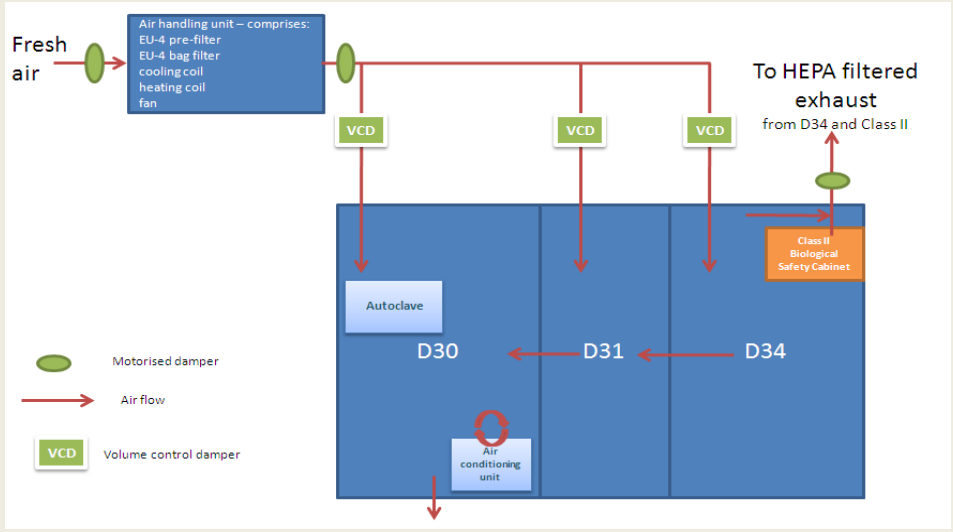


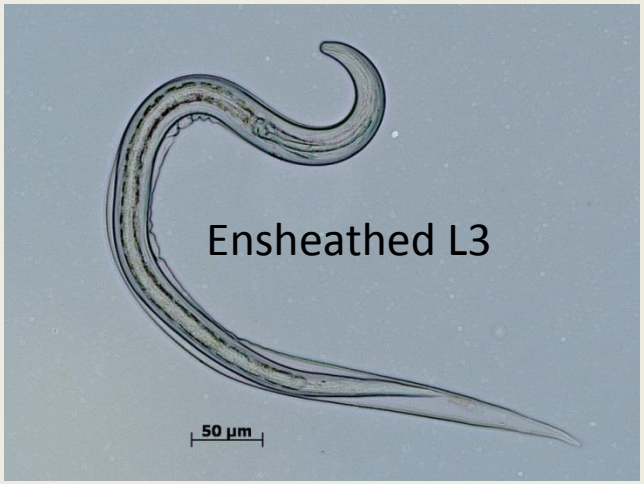
The free living phase of the life cycle is replicated in an approved clean room

Hookworm Production Unit

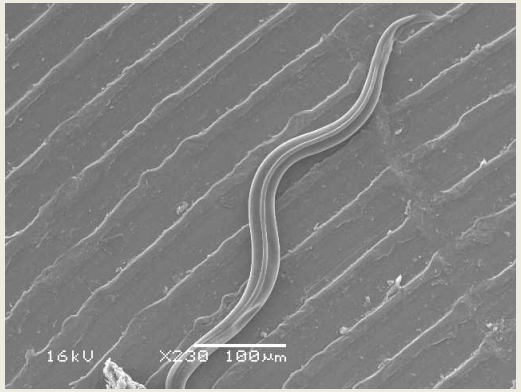


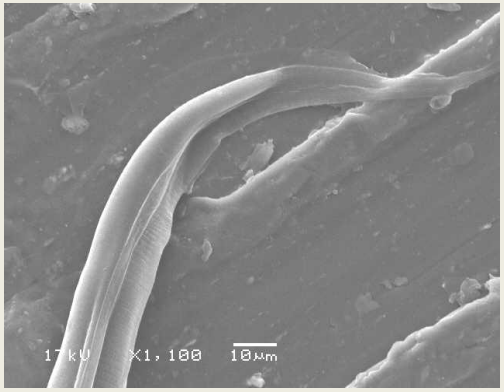


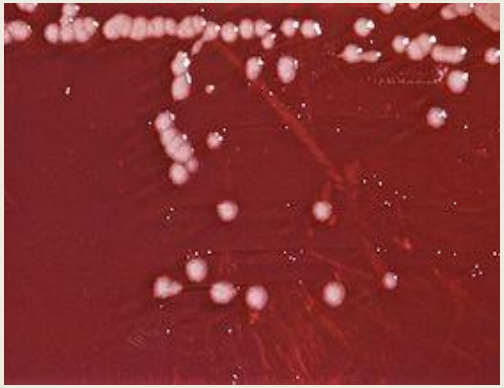




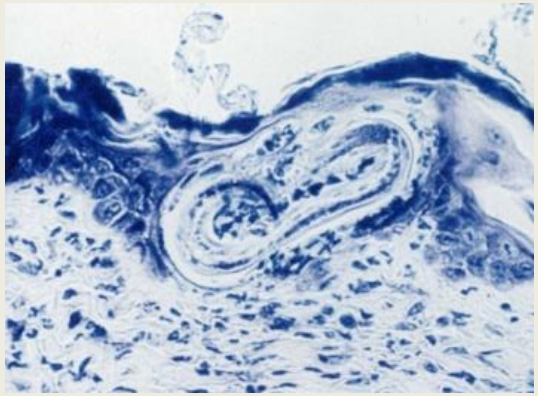
Cleanliness







Bacterial limits on supernates and larvae , for “topical application”.
Gentamicin and Amphotericin B added to faeces.
< 2 x 10^2 aerobes , 2 x 10^1 yeasts/moulds per dose.
Staph. aureus , *Pseudomonas aeruginosa* not permitted.

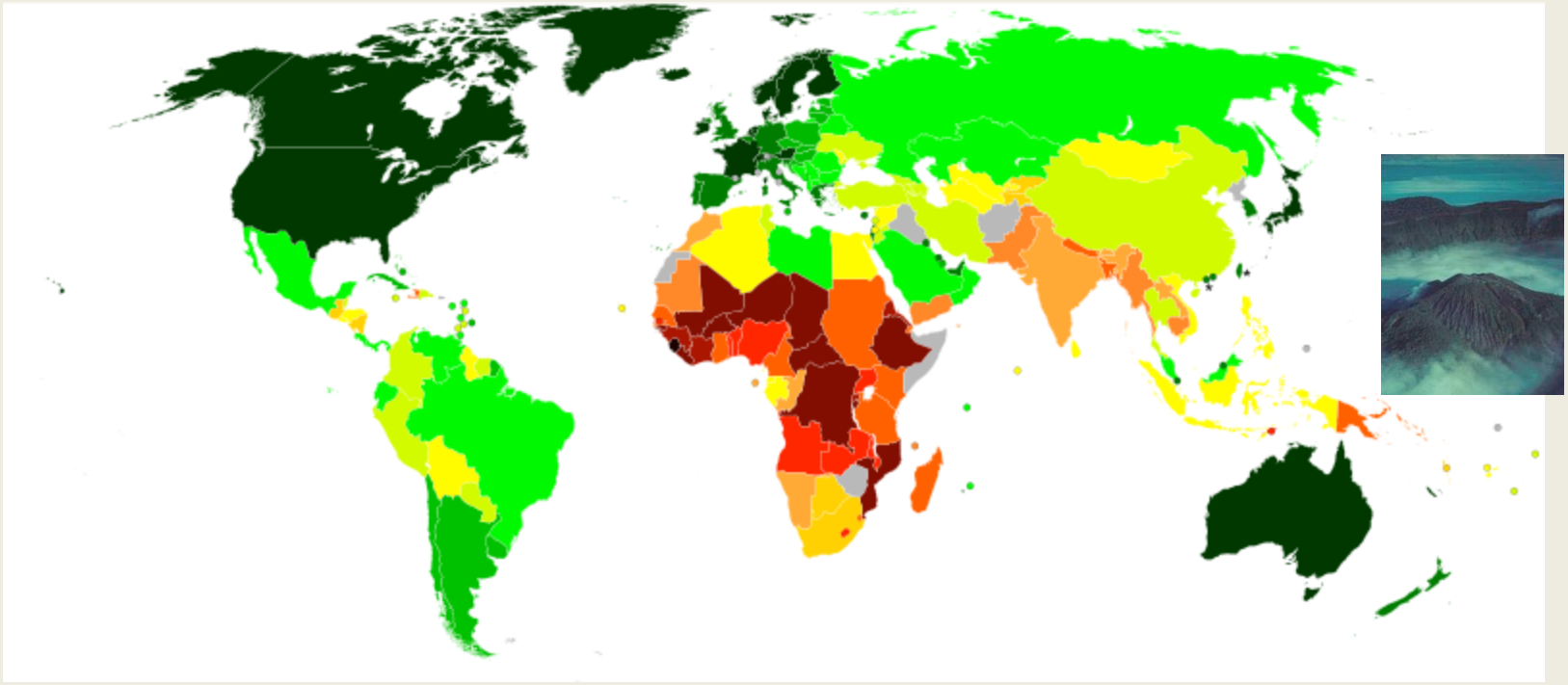


Safety Trials

- Designed to assess the safety of pulmonary transit
- Short duration trials (10 L3 for 12 weeks)
- Lung function measured throughout this time

Trial	Outcome	Published
PHASE 1	DOSE SELECTED	Am.J.Trop.Med.Hyg 75 914-920
PHASE 2 RHINITIS	SAFE	Clin. Exp. Allergy 39 1060-1068
PHASE 2 ASTHMA	SAFE	Clin. Exp. Allergy 40 299-306

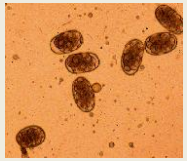
A well travelled isolate



PNG to UK to Queensland for therapeutic trials

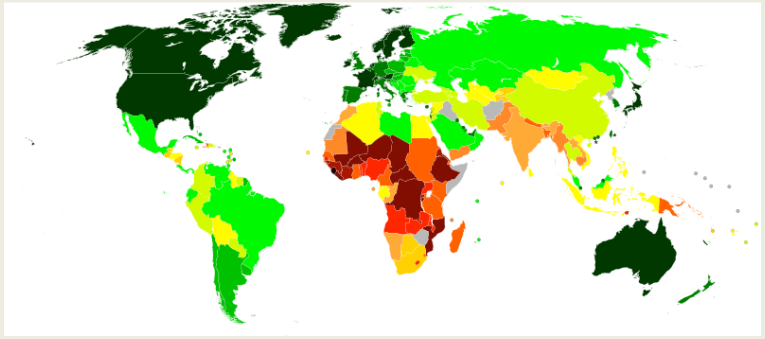
UK to Washington DC for vaccine trials

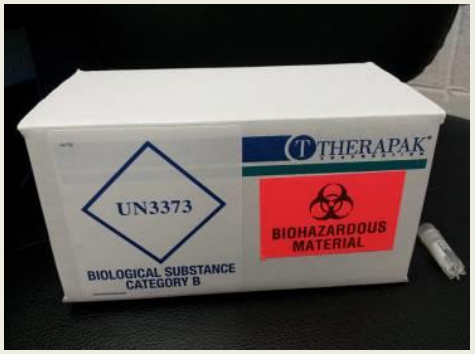
Sabin SA010 derived from cGMP batch 121102

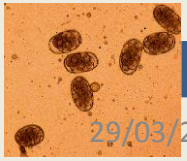


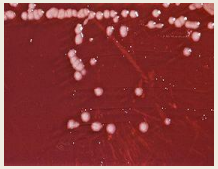
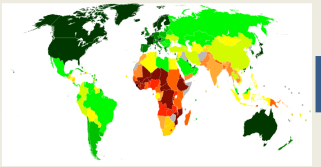

10 days in culture plus 15 days for microbiological clearance

97-100% viability 7 days post receipt







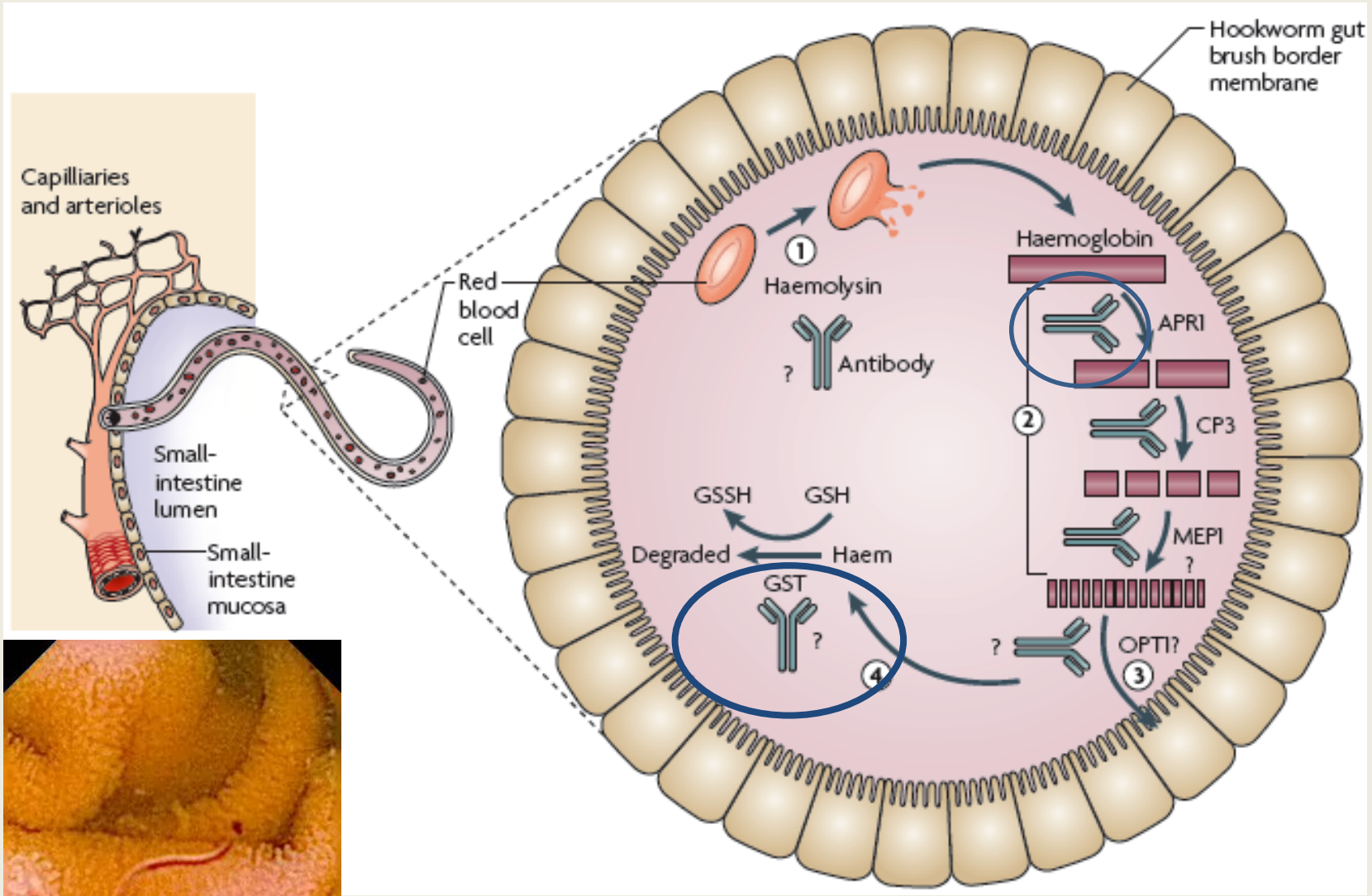

10 14 1 20

PHASE 1 : AN EXPERIMENTAL INFECTION STUDY OF DERMALLY-APPLIED *NECATOR AMERICANUS* HOOKWORM LARVAE IN HOOKWORM-NAÏVE ADULTS DOSE ESCALATION TO 75 L_3

Protocol Number:	SVI-CH-01
Version (Date):	4 (04 June 2014)
US FDA IND Number:	15752
GWU IRB Number:	061309
ClinicalTrials.gov ID:	NCT 01940757

Sponsor: Albert B. Sabin Vaccine Institute
2000 Pennsylvania Avenue, Suite 7100
Washington, DC 20006

PHASE 2.VACCINATION (safety evaluation passed in Phase 1)



Hookworms and Coeliac Disease
Preliminary Clinical Trial

Experimental hookworm infection and gluten microchallenge promote tolerance in celiac disease

John Croese, MD,[a,b]* Paul Giacomin, PhD,[b]* Severine Navarro, PhD,[b] Andrew Clouston, MD,[c] Leisa McCann, RN,[b] Annette Dougall, PhD,[b] Ivana Ferreira, BSc,[b] Atik Susianto, MD,[b] Peter O'Rourke, PhD,[d] Mariko Howlett, MD,[e] James McCarthy, MD,[d,e] Christian Engwerda, PhD,[d] Dianne Jones, BHSc,[f] and Alex Loukas, PhD[b] *Brisbane and Cairns, Australia*

JAMES COOK UNIVERSITY
AUSTRALIA

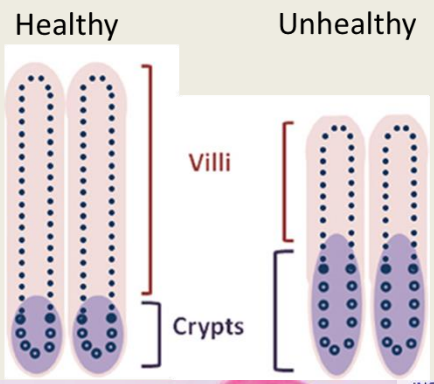
The Study

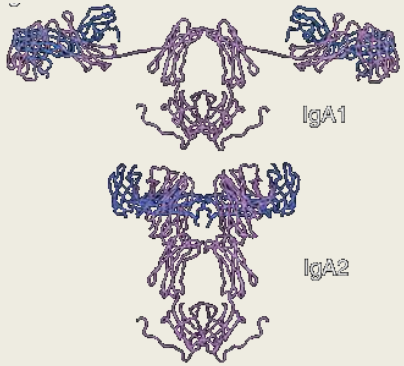
Clinical Markers

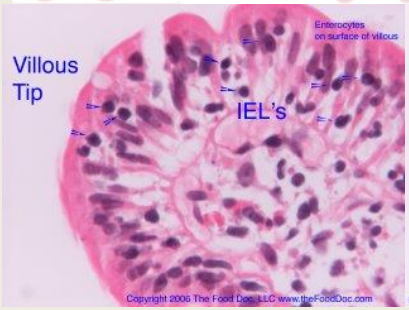
1. Villous height:crypt depth ratio
2. IgA – tissue transglutaminase

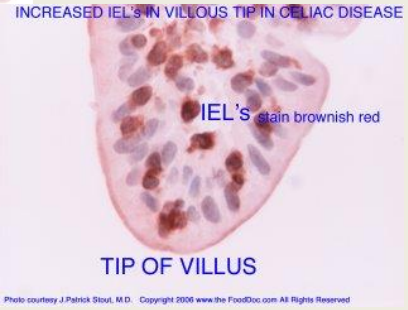
3. Lymphocyte (IEL & LPL)
4. T-cell IFNγ expression levels were monitored

5. Quality of life scores
6. Coeliac symptom indices









Method

- **Patients** 12 Started the Study, 8 completed
- **Age** 39 -67
- **Females** 9, **Males** 3
- **Years gluten free** 5 – 41 years

- ***N.americanus*** 20 iL3
- **Duration** 12 weeks
- **Gluten** 0.05 g to 3.00 g

Outcome

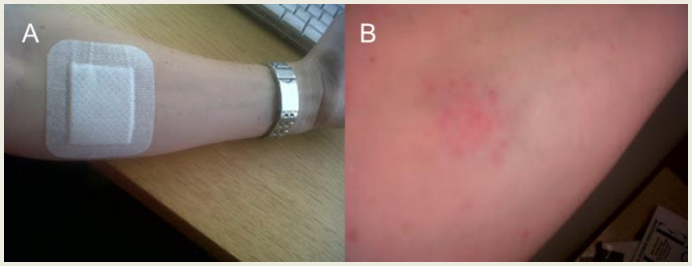
*"N. americanus and gluten micro challenge promoted tolerance and **stabilized or improved all tested indices of gluten toxicity** in coeliac disease subjects"*

- decreased intestinal inflammation
- alleviated symptoms
- enhanced quality of life
- increased tolerance to gluten by a factor of 60.

Equivalent to 60-75 straws of gluten containing spaghetti

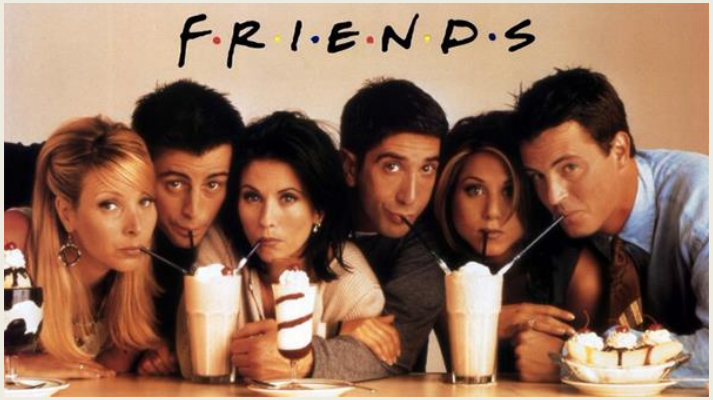
Testimonials

“It was incredibly pleasant. They just put a Band-Aid on your forearm and it just feels like they've got some Tabasco sauce on there.”



"I actually went out and I went to town and I had pizza and ice-cream, and salad sandwiches and Subway, just all the things I’ve missed for the last 15 years. And I was absolutely fine, I was terrific.”

"The worms take about four years before they die, unfortunately - and we call them our friends.” "Everyone in the trial called the worms our friends, so we don't want them to leave us, but they do."



ABC NEWS 24

Medical Daily

Science Daily

INTERNATIONAL BUSINESS TIMES

Healthline

DIGITAL JOURNAL

6minutes
of interesting stuff for doctors today

afr.com

FINANCIAL REVIEW

A focus on... - October 2015 eXG

A "living drug" for coeliac disease

The main focus of this year's Research Conference was therapeutic advances in coeliac disease. One novel therapy that was not represented at the conference is hookworm.

Necator americanus, a "living drug", is a hookworm from humans, which was recently used in a small clinical trial in Australia as a potential therapy for people with coeliac disease [1].

Participants diagnosed with coeliac disease were treated with hookworms and asked to eat gluten in increasing amounts. The maximum amount was equivalent to a bowl of gluten containing pasta, every day, for two weeks.

Treatment with hookworm:

- decreased intestinal inflammation
- alleviated common unwanted symptoms of coeliac disease
- enhanced quality of life and
- increased tolerance to gluten by a factor of 60.

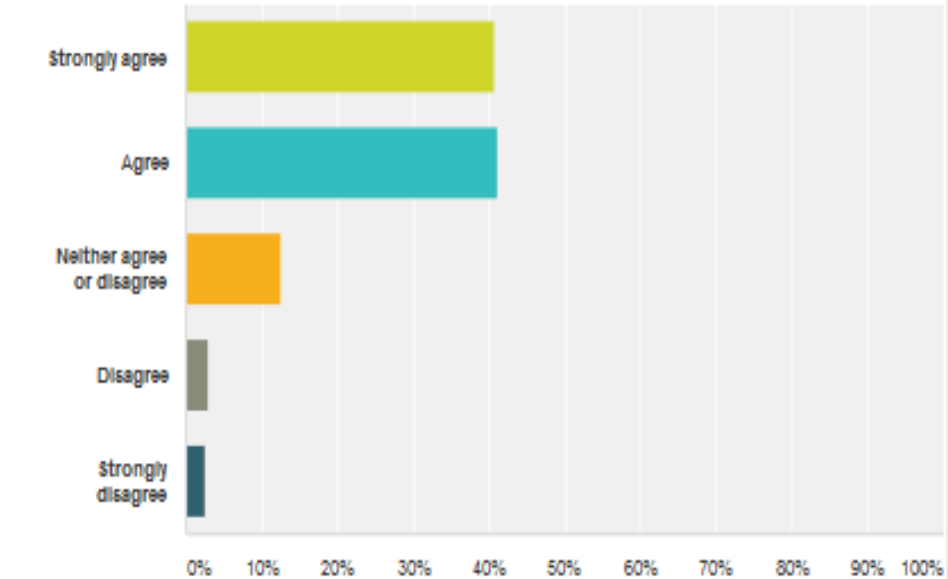
The findings suggest that hookworm treatment, combined with gradually increased amounts of dietary gluten, promotes immune regulation and tolerance to gluten in people with coeliac disease.

Newsletter

- Online questionnaire
- 60,000 approached
- 280 replies

"I feel that further exploring the research in hookworm therapy could potentially improve the lives of people living with coeliac disease"

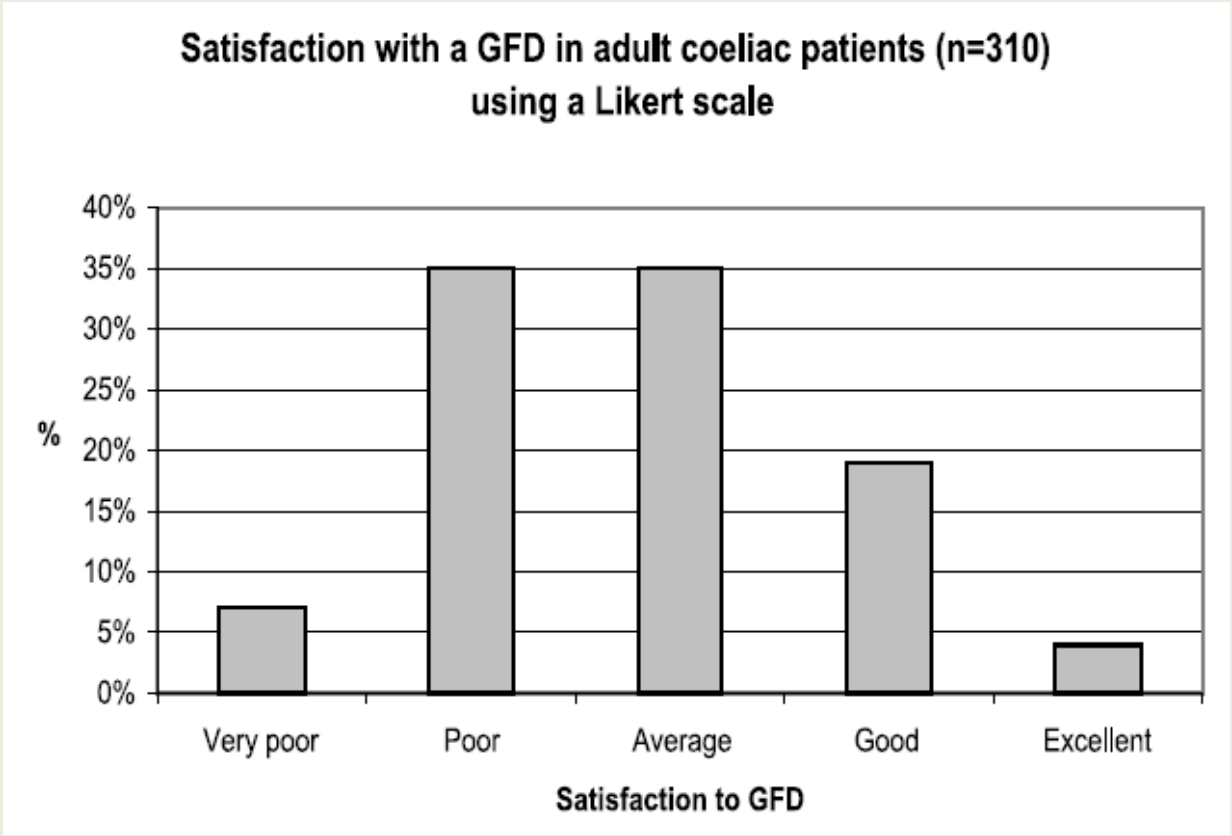
- **82% Strongly Agree/ Agree**



Answer Choices	Responses	
Strongly agree	40.77%	95
Agree	41.20%	96
Neither agree or disagree	12.45%	29
Disagree	3.00%	7
Strongly disagree	2.58%	6
Total		233

Are Patients with Coeliac Disease Seeking Alternative Therapies to a Gluten-free Diet?

Imran Aziz, Kate E Evans, Vasiliki Papageorgiou, David S Sanders
Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK



Future plans

- Maintenance of the life cycle
- In the event clinical efficacy is demonstrated (2018-2019)……..
- Approved iL3 can be readily available to UK patients

MHRA
Regulating Medicines and Medical Devices

FDA

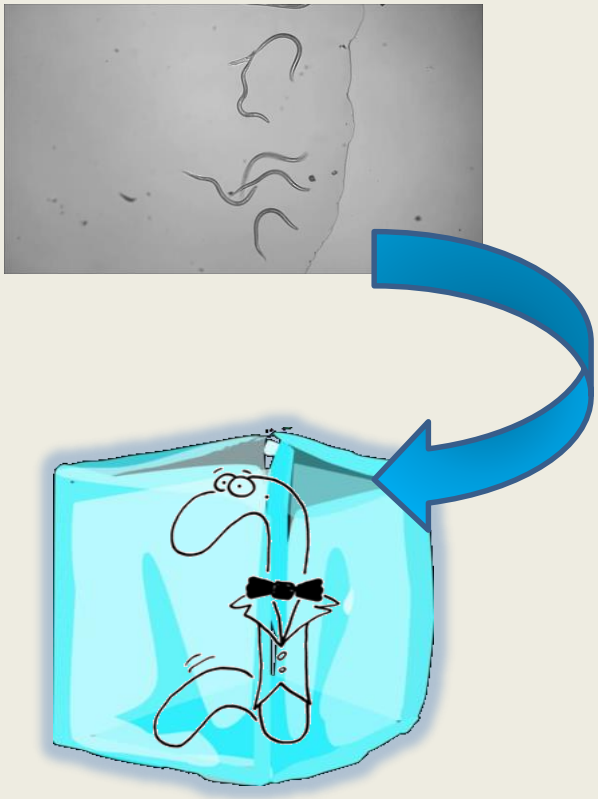
Maintenance of resource strategies include:

1) Continued maintenance in donors

- Nottingham IMPACT campaign (~12.5k)

2) Cryopreservation

- Freeze nematodes, thaw when required
- Full economic cost £ 148,050
- Cost to funder £ 47,263



The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Summary

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

Hookworms have the potential to treat immune diseases

Infection has been successfully applied to coeliac disease and we continue to explore its potential in MS

However, with 700 million hyper-infected with *Necator americanus* vaccine development is equally important

MS Multiple Sclerosis Society

The Forman Hardy Charitable Trust

SABIN VACCINE INSTITUTE

wellcome trust

Impact The Nottingham Campaign

NIH

Thank you

- Coeliac UK
- Féaron Cassidy, Isobel Ford , GUTS
- Dr Heidi Urwin
- University of Nottingham
- For Further Information

gail.atkinson@nottingham.ac.uk

Coeliac uk
support – campaigns – research

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