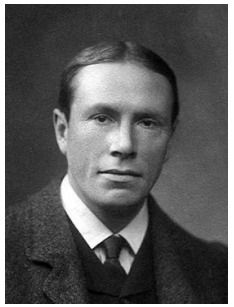
# From fruit fly development to cancer therapy: a journey through the life sciences

**Philip Ingham** FRS HonFRCP

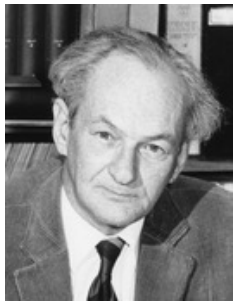
Raymond Schinazi and Family Chair of Life Sciences
Department of Life Sciences
University of Bath

UNIVERSITY OF CAMBRIDGE
Department of Genetics

Established 1912


Reginald Punnet


RA Fisher


John Thoday

**Natural Sciences Tripos Part II Genetics Class, 1976-77**

*Proc. Nat. Acad. Sci. USA*
Vol. 71, No. 5, pp. 1743–1747, May 1974

## Replication and Transcription of Eukaryotic DNA in *Escherichia coli*

**(restriction/plasmid/transformation/recombination/ribosomal DNA)**

JOHN F. MORROW*††, STANLEY N. COHEN†, ANNIE C. Y. CHANG†, HERBERT W. BOYER§, HOWARD M. GOODMAN¶, AND ROBERT B. HELLING§||

Departments of *Biochemistry and †Medicine, Stanford University School of Medicine, Stanford, California 94305; and Departments of §Microbiology and ¶Biochemistry and Biophysics, University of California, San Francisco, Calif. 94143

*Communicated by Joshua Lederberg, January 4, 1974*

**ABSTRACT** **Fragments of amplified *Xenopus laevis* DNA, coding for 18S and 28S ribosomal RNA and generated by *Eco*RI restriction endonuclease, have been linked *in vitro* to the bacterial plasmid pSC101; and the recombinant molecular species have been introduced into *E. coli* by transformation. These recombinant plasmids, containing both eukaryotic and prokaryotic DNA, replicate stably in *E. coli*. RNA isolated from *E. coli* minicells harboring the plasmids hybridizes to amplified *X. laevis* rDNA.**

Vol. 76, No. 1, 1977 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS

## A RAPID PROCEDURE FOR PURIFICATION OF EcoRI ENDONUCLEASE

János Sümegi, Danielle Breedveld, Paul Hossenlopp and Pierre Chambon

Laboratoire du CNRS de Biologie Moléculaire des Eucaryotes
et Groupe de Recherche 44 de l'INSERM, Faculté de Médecine
Strasbourg - France

Received March 14,1977

*Proc. Natl. Acad. Sci. USA*
Vol. 74, No. 12, pp. 5463–5467, December 1977
Biochemistry

## DNA sequencing with chain-terminating inhibitors

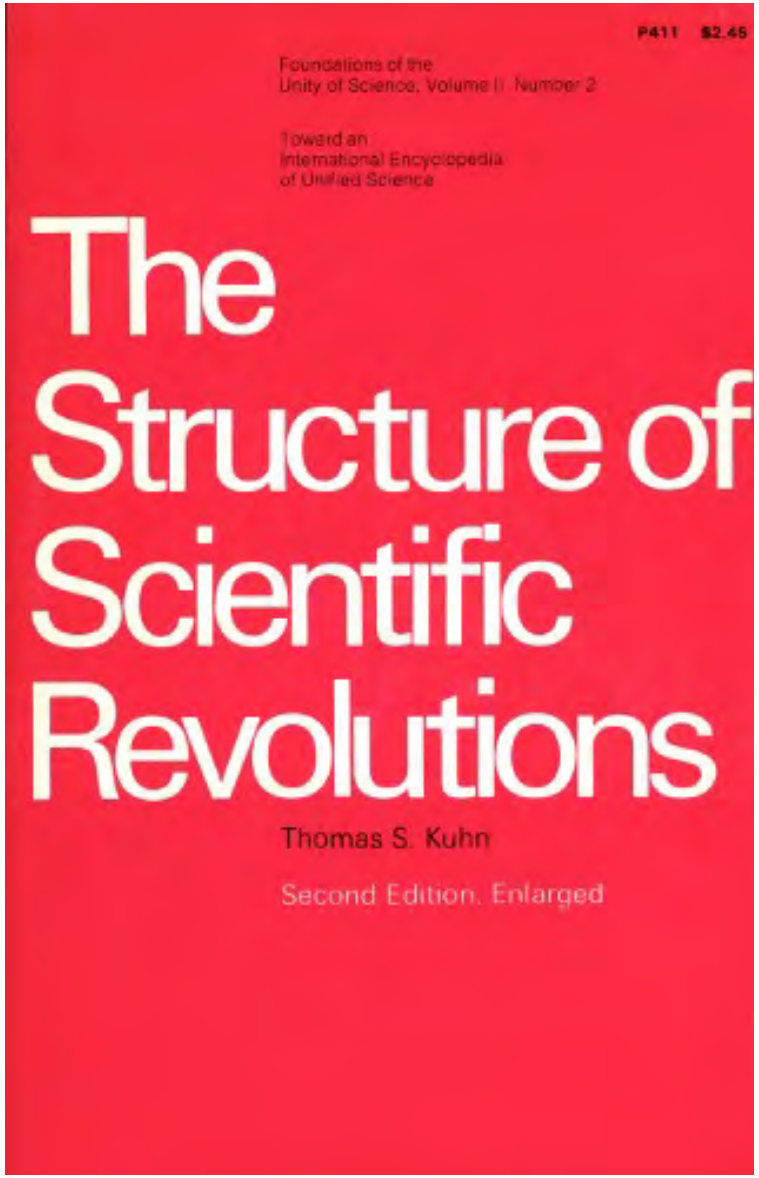
**(DNA polymerase/nucleotide sequences/bacteriophage φX174)**

F. SANGER, S. NICKLEN, AND A. R. COULSON

Medical Research Council Laboratory of Molecular Biology, Cambridge CB2 2QH, England

*Contributed by F. Sanger, October 3, 1977*

In general, sequences of from 15 to about 200 nucleotides from the priming site can be determined with reasonable accuracy using a single primer. Frequently it is possible to read the gels further and, on occasions, a sequence of about 300 nucleotides from the priming site has been determined. Oc-


P411 $2.45
Foundations of the
Unity of Science, Volume II Number 2
Toward an
International Encyclopedia
of Unified Science
The
Structure of
Scientific
Revolutions
Thomas S. Kuhn
Second Edition, Enlarged

# E.B. Lewis and the discovery of the bithorax complex (BX-C)

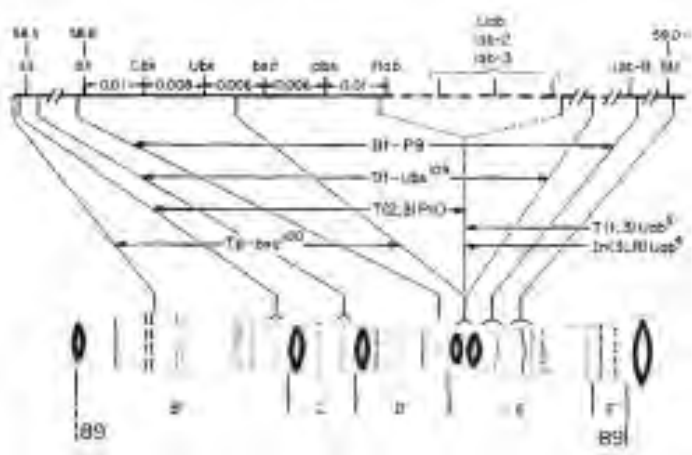
Nature Vol. 276 7 December 1978



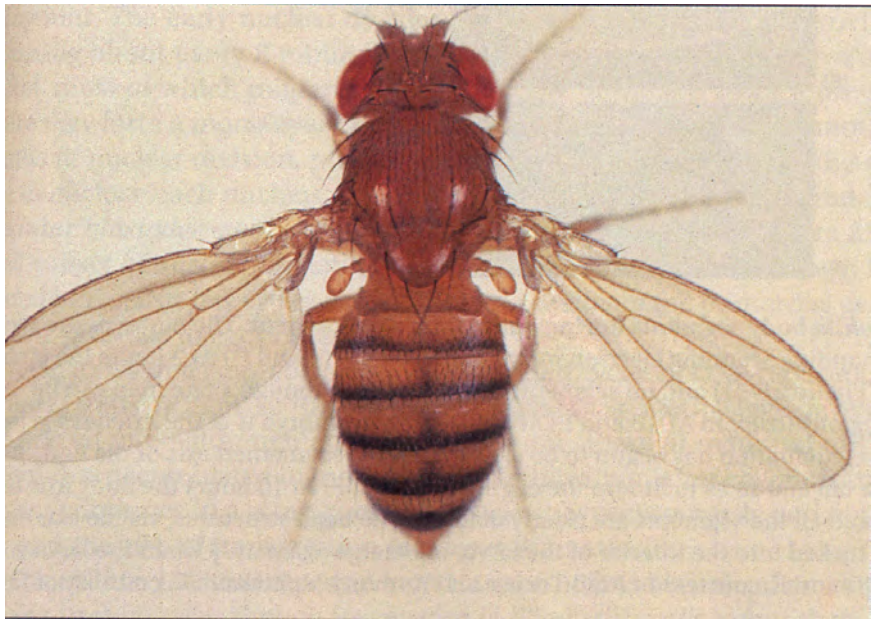
review article

## A gene complex controlling segmentation in *Drosophila*

**E. B. Lewis**
Division of Biology, California Institute of Technology, Pasadena, California 91125



Alfred Sturtevant

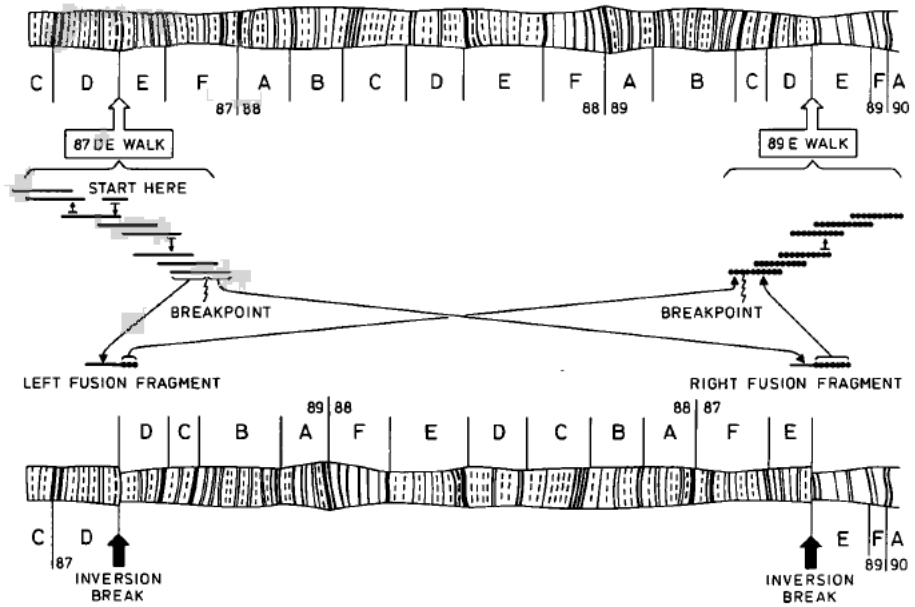


T H Morgan

# The breakthrough: positional cloning of genes with unknown products

## Chromosomal Walking and Jumping to Isolate DNA from the *Ace* and *rosy* Loci and the Bithorax Complex in *Drosophila melanogaster*

WELCOME BENDER†, PIERRE SPIERER‡ AND DAVID S. HOGNESS§

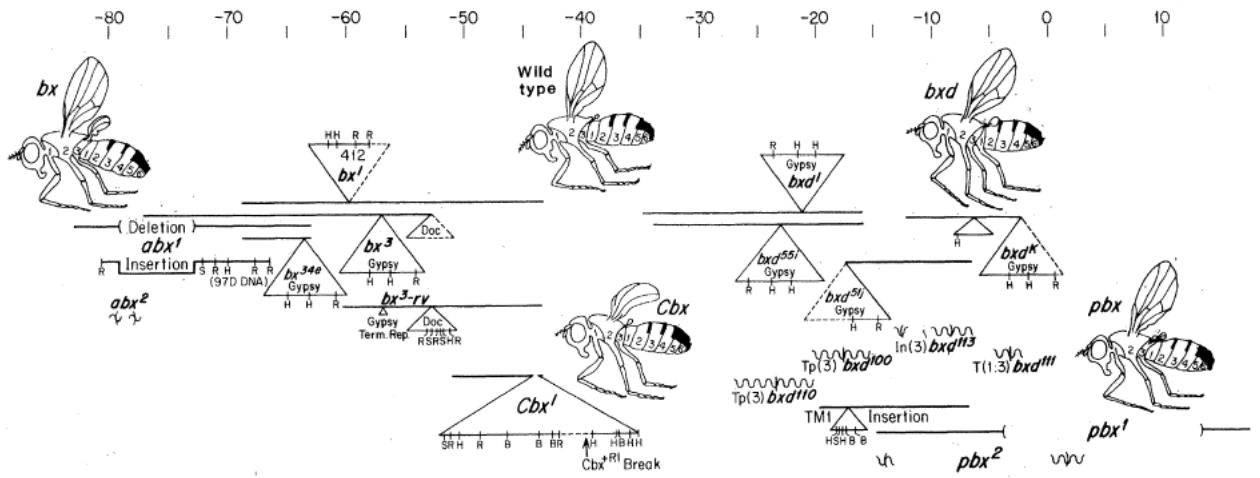



SCIENCE, VOL. 221 1 JULY 1983

**RESEARCH ARTICLE**

## Molecular Genetics of the Bithorax Complex in *Drosophila melanogaster*

Welcome Bender, Michael Akam, François Karch
Philip A. Beachy, Mark Peifer, Pierre Spierer
E. B. Lewis, David S. Hogness



# Hox genes provide the first evidence for conservation of developmental mechanisms in animal evolution

Cell, Vol. 37, 409–414, June 1984, Copyright © 1984 by MIT

0092-8674/84/060409-06 $02.00/0

## Cloning of an X. laevis Gene Expressed during Early Embryogenesis Coding for a Peptide Region Homologous to Drosophila Homeotic Genes

**Andrés E. Carrasco, William McGinnis, Walter J. Gehring, and Eddy M. De Robertis**
Department of Cell Biology
Biozentrum, University of Basel
Klingelbergstr. 70
CH-4056 Basel, Switzerland

**Results**

**The X. laevis Genome Contains Several Single-Copy Restriction Fragments Homologous to Homeo Box Sequences**

In order to determine whether the frog genome contained

Cell, Vol. 38, 667–673, October 1984, Copyright © 1984 by MIT

0092-8674/84/100667-07 $02.00/0

## Human DNA Sequences Homologous to a Protein Coding Region Conserved between Homeotic Genes of Drosophila

**Michael Levine,* Gerald M. Rubin, and Robert Tjian**
Department of Biochemistry
University of California
Berkeley California 94720

itself to the type of analysis that is necessary to identify such key developmental regulatory genes. By contrast, a number of loci in Drosophila have been genetically defined and are implicated in directing the acquisition of distinct body segments (reviewed by Duweneel, 1976). The ge-

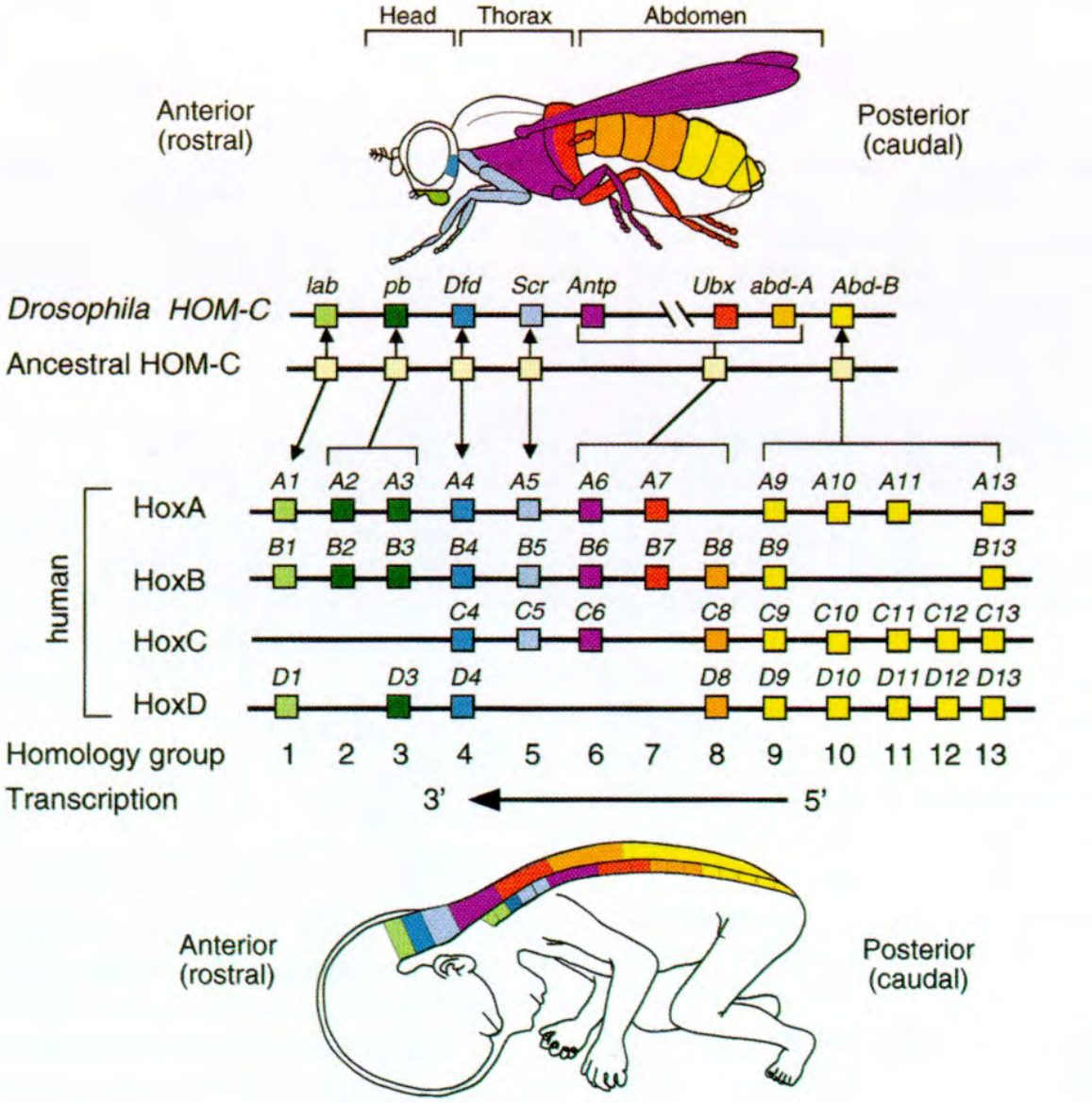
Cell, Vol. 43, 9–18, November 1985, Copyright © 1985 by MIT

0092–8674/85/110009–10 $02.00/0

## Homeo Box Gene Complex on Mouse Chromosome 11: Molecular Cloning, Expression in Embryogenesis, and Homology to a Human Homeo Box Locus

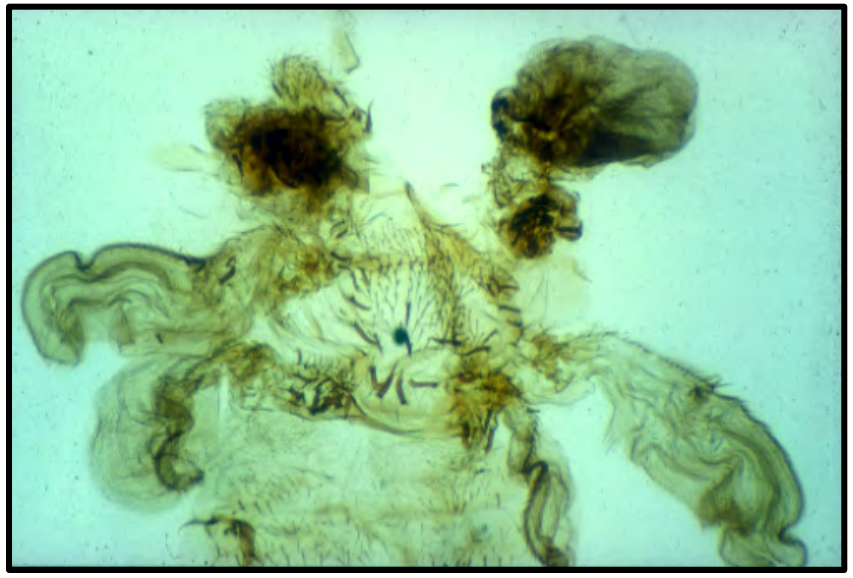
**Charles P. Hart,* Alexander Awgulewitsch,* Abraham Fainsod,* William McGinnis,† and Frank H. Ruddle***
*Department of Biology
†Department of Molecular Biophysics and Biochemistry
Yale University
New Haven, Connecticut 06511

of the homeo box sequences of *Antp*, *Ubx*, and *ftz* showed approximately 85% homology between the copies. A search of the Dayoff protein sequence data bank showed significant similarities between a consensus homeo domain sequence and the yeast mating type proteins a-1 and α-2 (Shepherd et al., 1984; Laughton and Scott, 1984). These proteins are thought to regulate other genes in-




*Mark et al (1997) Pediatric Research*

UNIVERSITY OF SUSSEX AT BRIGHTON



Molec. gen. Genet. 179, 607–614 (1980)

# *Trithorax:* A New Homoeotic Mutation of *Drosophila melanogaster* Causing Transformations of Abdominal and Thoracic Imaginal Segments

## I. Putative Role During Embryogenesis

Philip Ingham and Robert Whittle

Communicated by W. Gehring

Received February 25 / July 7, 1980

NATURE VOL. 306 8 DECEMBER 1983

# Differential expression of *bithorax complex* genes in the absence of the *extra sex combs* and *trithorax* genes

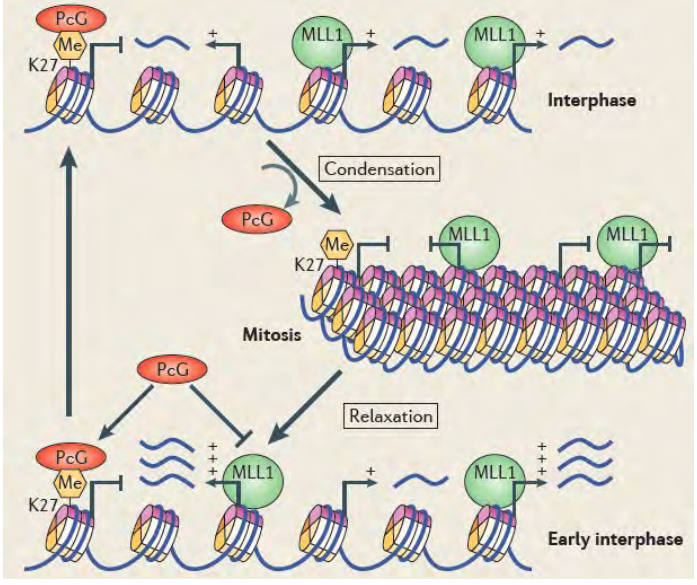
**P. W. Ingham**

Imperial Cancer Research Fund, Mill Hill Laboratories, London NW7 1AD, UK

NATURE REVIEWS | MOLECULAR CELL BIOLOGY

# Trithorax group proteins: switching genes on and keeping them active

*Bernd Schuettengruber*§, Anne-Marie Martinez*‡§, Nicola Iovino* and Giacomo Cavalli**



# EMBO Molecular and developmental biology of *Drosophila* Workshop 1980

The Orthodox Academy, Kolymbari, Crete

Christiane Nüsslein-Volhard
& Eric Wieschaus

EMBL, Heidelberg

# Landmark *Nature* paper that represents a paradigm shift in the field

*Nature* Vol. 287 30 October 1980

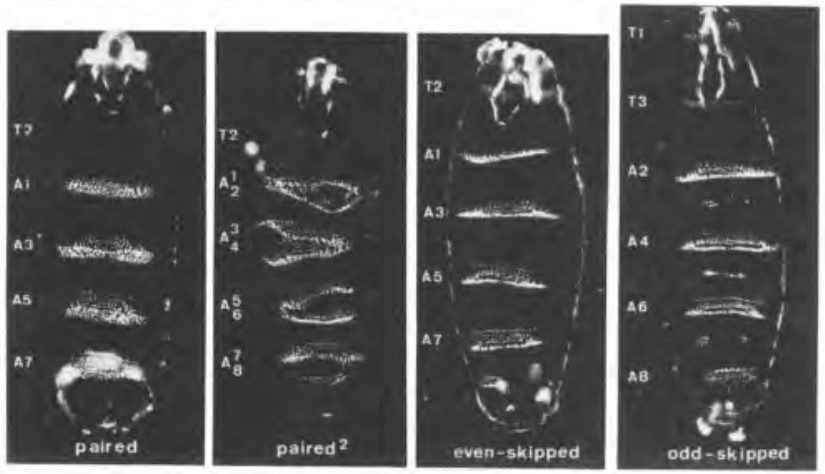
## Mutations affecting segment number and polarity in *Drosophila*

**Christiane Nüsslein-Volhard & Eric Wieschaus**

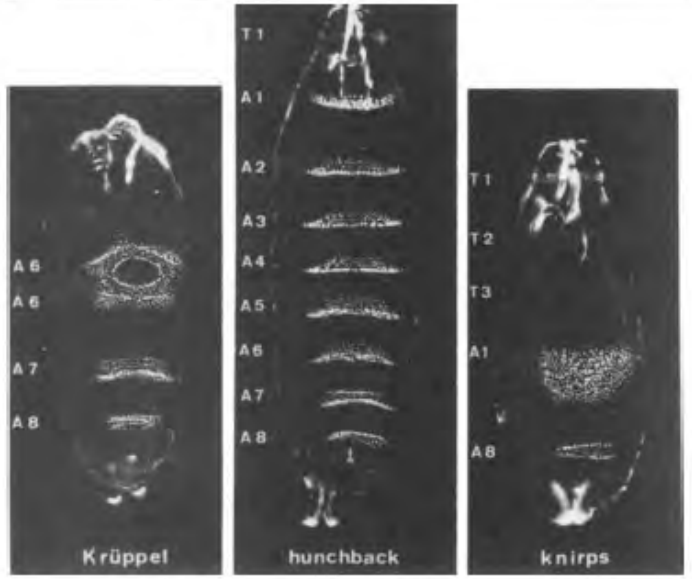
European Molecular Biology Laboratory, PO Box 10.2209, 69 Heidelberg, FRG

*In systematic searches for embryonic lethal mutants of* Drosophila melanogaster *we have identified 15 loci which when mutated alter the segmental pattern of the larva. These loci probably represent the majority of such genes in* Drosophila. *The phenotypes of the mutant embryos indicate that the process of segmentation involves at least three levels of spatial organization: the entire egg as developmental unit, a repeat unit with the length of two segments, and the individual segment.*









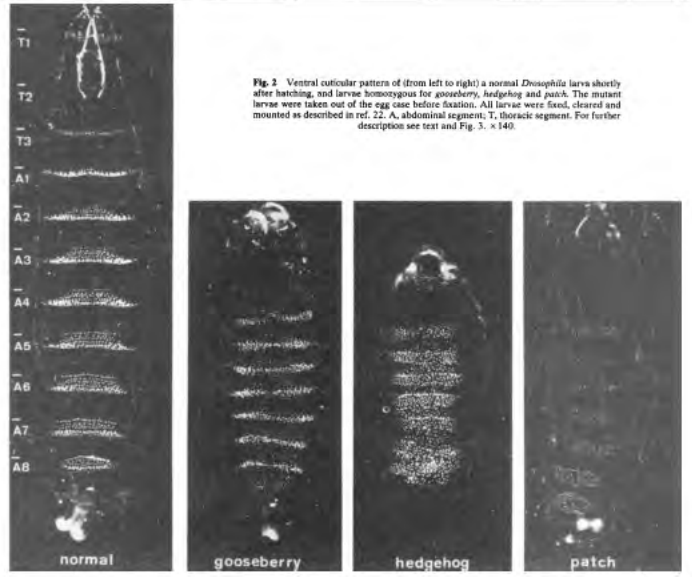




Fig. 2 Ventral cuticular pattern of (from left to right) a normal *Drosophila* larva shortly after hatching, and larvae homozygous for *gooseberry*, *hedgehog* and *patch*. The mutant larvae were taken out of the egg case before fixation. All larvae were fixed, cleared and mounted as described in ref. 22. A, abdominal segment; T, thoracic segment. For further description see text and Fig. 3. ×140.

# Visualising Gene expression in whole organisms for the first time

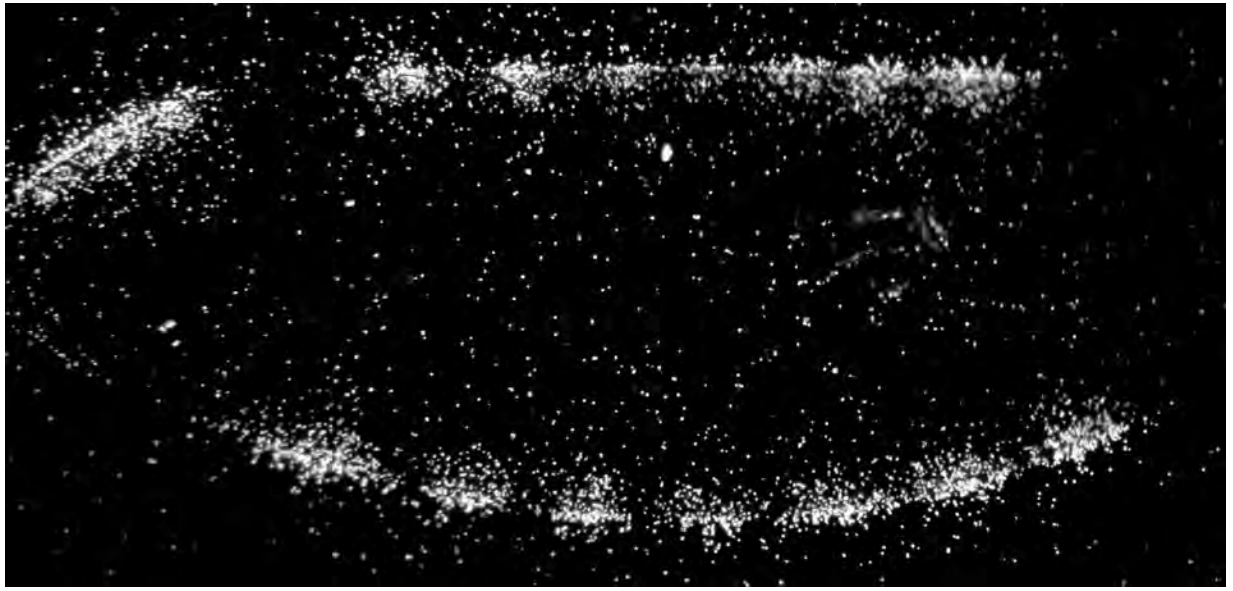
Reprinted from Nature, Vol. 318, No. 6045, pp. 439-445, 5 December 1985


## Transcription pattern of the *Drosophila* segmentation gene *hairy*

P. W. Ingham, K. R. Howard & D. Ish-Horowicz

Developmental Genetics Laboratory, Imperial Cancer Research Fund, Mill Hill Laboratories, Burtonhole Lane, London NW7 1AD, UK*

*Segmentation of the* Drosophila *embryo requires expression of the pair-rule genes, mutations of which cause reiterated deletions in alternate segments along the antero-posterior body axis. We find that transcripts of one such gene,* hairy, *accumulate in eight distinct regions of the early embryo. This pattern of expression is compared with that of another pair-rule gene,* fushi tarazu, *and its dependence on maternally expressed genes is described.*



Imperial Cancer Research Fund

# The convergence of two fields: cancer biology and developmental biology

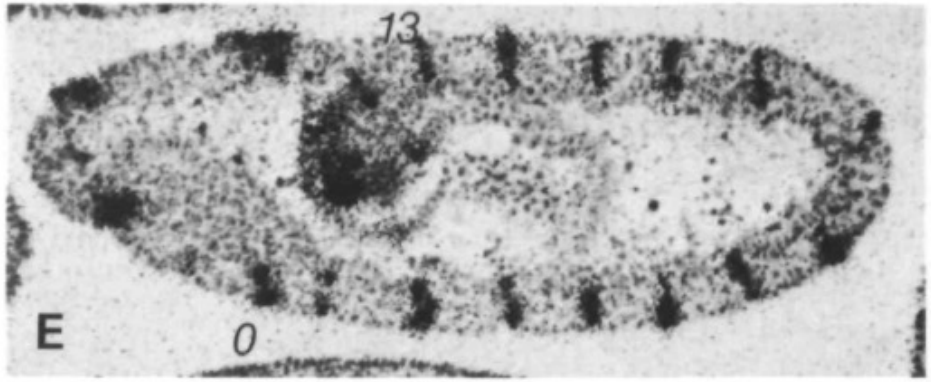
NATURE VOL. 307 12 JANUARY 1984 ARTICLES 131

## Mode of proviral activation of a putative mammary oncogene (*int*-1) on mouse chromosome 15

**Roel Nusse*, Albert van Ooyen*, David Cox†, Yuen Kai T. Fung‡ & Harold Varmus‡**

* Department of Virology, Netherlands Cancer Institute, Antoni van Leeuwenhoekhuis, Plesmanlaan 121, Amsterdam, The Netherlands
† Department of Pediatrics and ‡ Department of Microbiology, University of California, San Francisco, California 94143, USA

*Most mammary carcinomas induced in C3H mice by the mouse mammary tumour virus (MMTV) bear a new proviral insertion within a highly conserved locus on chromosome 15 called* int-*1. A transcriptional unit within this locus is inactive in all tested normal tissues but expressed at low levels in mammary tumours with proviral insertions positioned on either the 5′ and 3′ sides of the gene. Transcription of the proviruses proceeds away from* int-*1; thus an indirect mechanism appears to activate expression of this putative oncogene.*




Cell, Vol. 50, 649–657, August 14, 1987, Copyright © 1987 by Cell Press

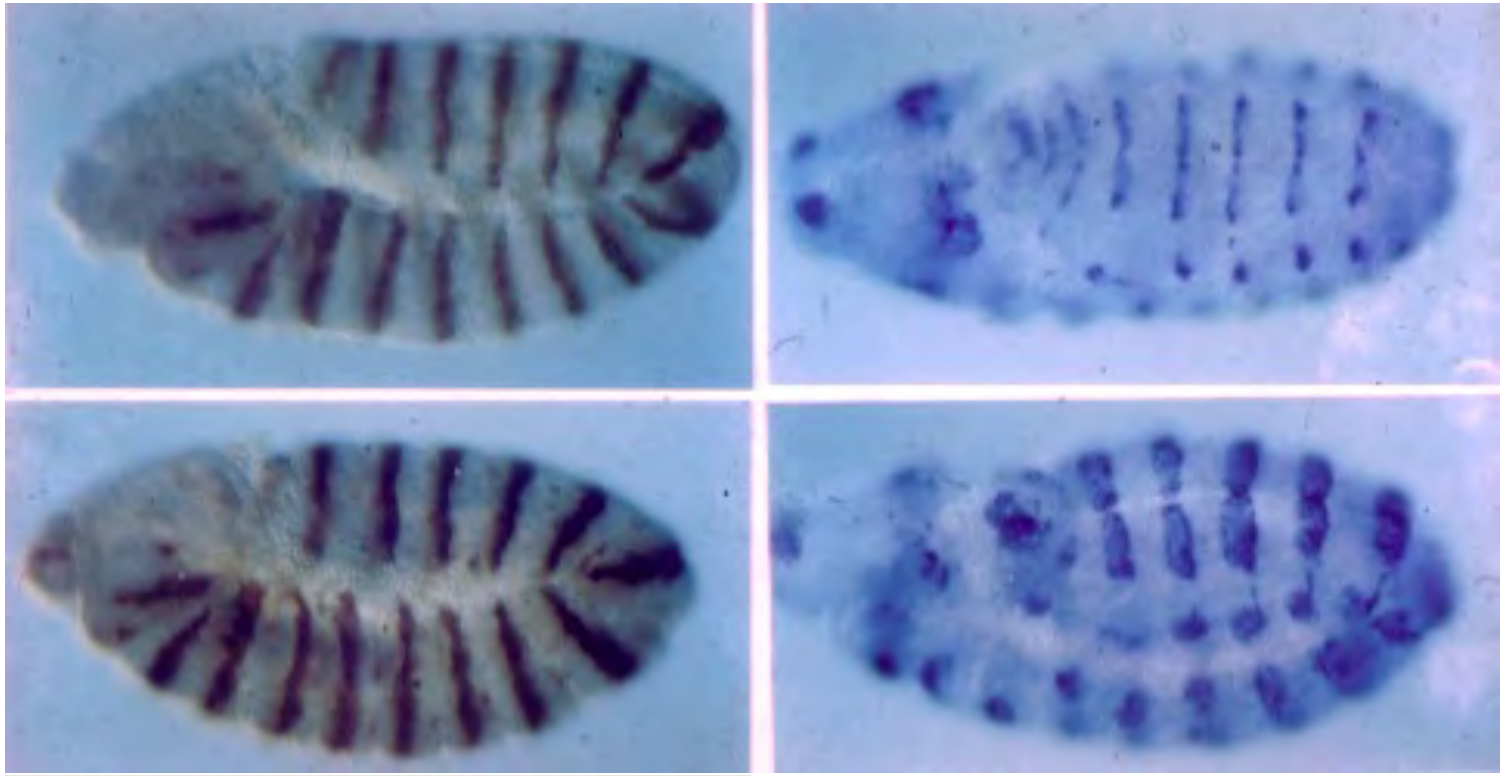
## The Drosophila Homolog of the Mouse Mammary Oncogene *int*-1 Is Identical to the Segment Polarity Gene *wingless*

**Frans Rijsewijk,* Marcus Schuermann,† Els Wagenaar,* Paul Parren,* Detlef Weigel,‡ and Roel Nusse***

* Division of Molecular Biology
Netherlands Cancer Institute
Plesmanlaan 121
1066CX Amsterdam, The Netherlands
† European Molecular Biology Laboratory
Mayerhofstrasse 1
6900 Heidelberg, Federal Republic of Germany
‡ Max-Planck-Institut für Entwicklungsbiologie
Spemannstrasse 35/II
D-7400 Tübingen, Federal Republic of Germany

rus. *int*-1 encodes a protein of 370 amino acids characterized by a high content of cysteine residues and a hydrophobic leader (van Ooyen and Nusse, 1984; Fung et al., 1985). This structure indicates that the protein may be secreted from the cells and serve in intercellular communication. In tumors with proviral insertions at *int*-1, the protein-encoding domain is always intact, illustrating the selective growth advantage conferred on mammary cells with an activated *int*-1 allele (van Ooyen and Nusse, 1984). Direct evidence for the oncogenic potential of *int*-1 has been provided by gene-transfer experiments showing that overexpression of the gene leads to the morphological transformation and tumorigenicity of various mammary

# Discovery that the *patched* gene is required to repress transcription of the proto-oncogene *wingless*



engrailed

wingless

*Wild type*

*patched*

Martinez-Arias, Baker and Ingham (1988) *Development*

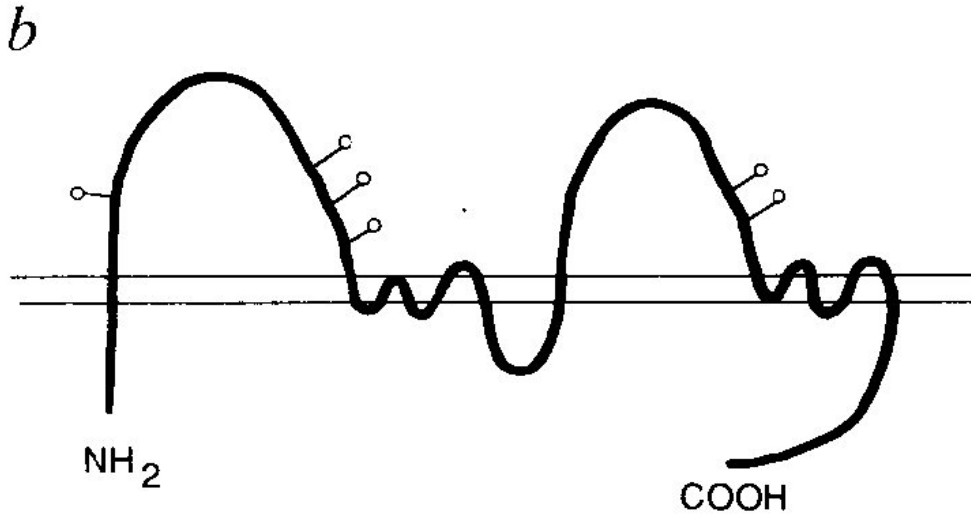
# Molecular cloning of the *patched* gene provided a key insight into its function

Reprinted from Nature, Vol. 341, No. 6242, pp. 508-513, 12th October, 1989


## A protein with several possible membrane-spanning domains encoded by the *Drosophila* segment polarity gene *patched*

**Y. Nakano, I. Guerrero*, A. Hidalgo, A. Taylor, J. R. S. Whittle† & P. W. Ingham**

Molecular Embryology Laboratory, ICRF Developmental Biology Unit, Department of Zoology, Oxford OX1 3PS, UK
† School of Biological Sciences, University of Sussex, Falmer, East Sussex BN1 9QG, UK

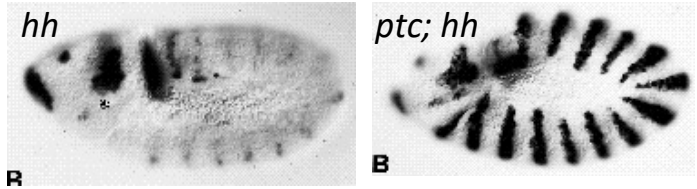



NATURE · VOL 353 · 12 SEPTEMBER 1991

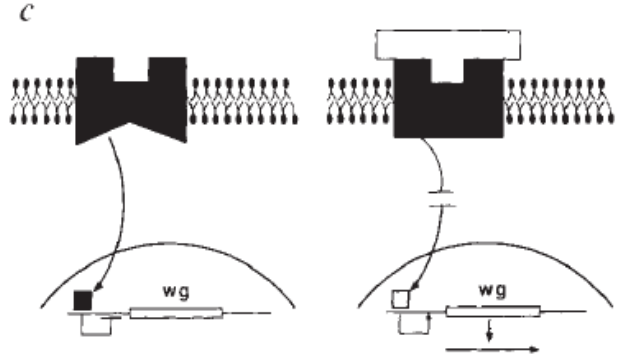
## Role of the *Drosophila patched* gene in positional signalling

**P. W. Ingham, A. M. Taylor & Y. Nakano**

Molecular Embryology Laboratory, ICRF Developmental Biology Unit, Department of Zoology, South Parks Road, Oxford OX1 3PS, UK




*wg* expression




**We suggest that the *patched* protein may itself be the receptor for this signal, implying that this is an unusual mechanism of ligand-dependent receptor inactivation.**

# Identification of the components of the Hedgehog signal transduction pathway by genetic analysis

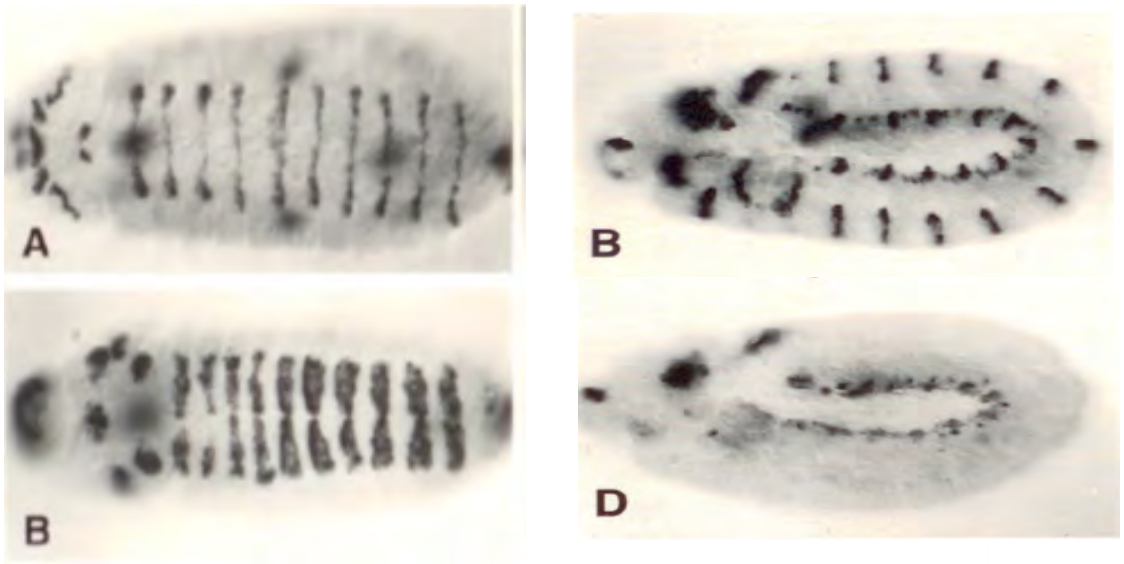
Development 1993 Supplement, 115-124 (1993)
Printed in Great Britain © The Company of Biologists Limited 1993

## Genetic analysis of *hedgehog* signalling in the *Drosophila* embryo

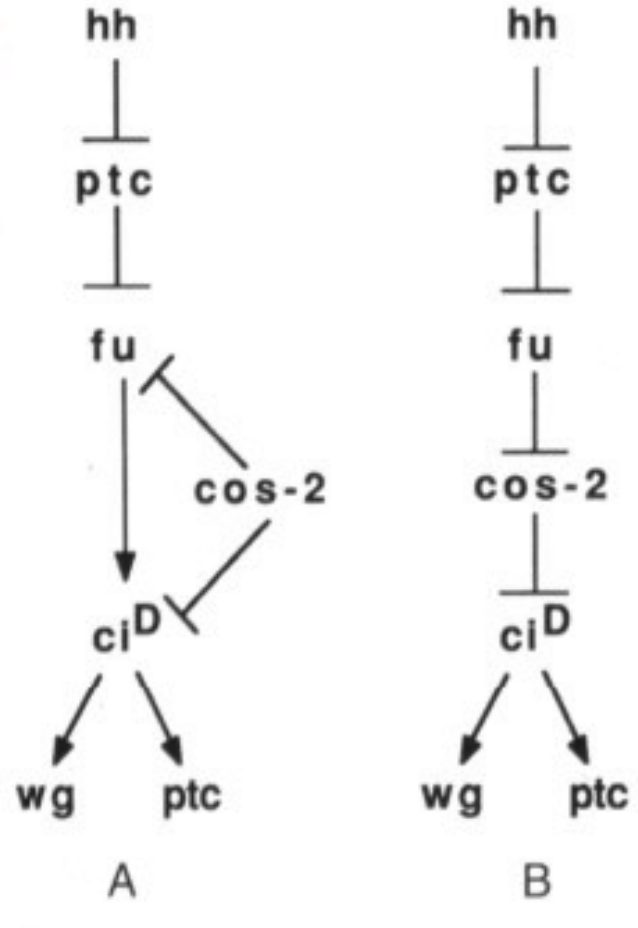
**A. J. Forbes, Y. Nakano†, A. M. Taylor and P. W. Ingham***

Molecular Embryology Laboratory, ICRF Developmental Biology Unit, Department of Zoology, South Parks Road, Oxford, OX1 3PS, UK

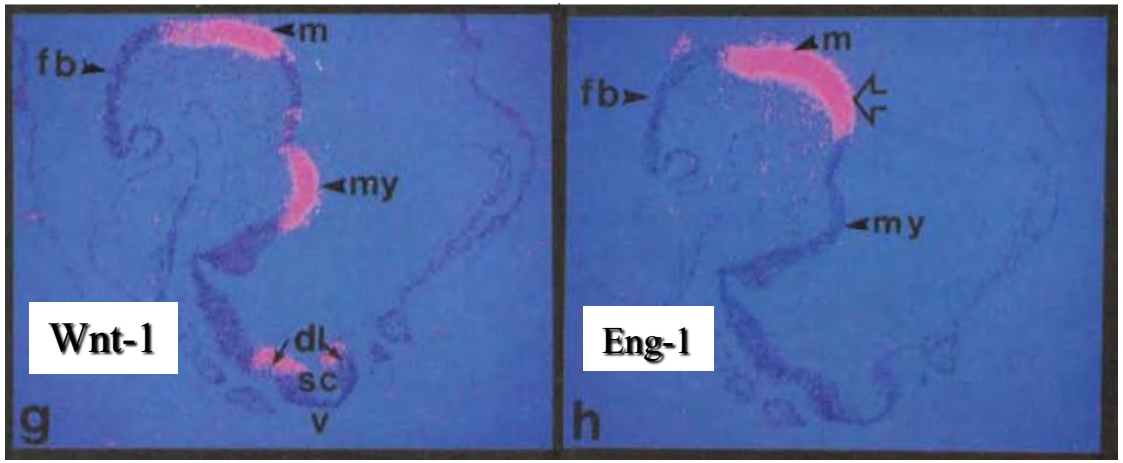
\+ +



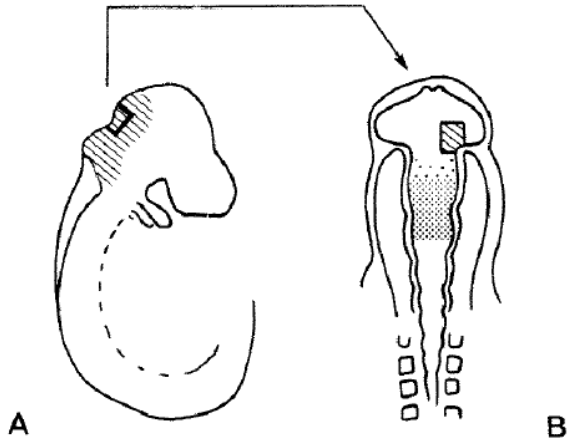

*cos2* *fused*



# Have signalling networks been conserved through evolution?




**Wilkinson, Bailes & McMahon *Cell* (1987)**




**Bally-Cuif et al *Development* (1992)**

## Human Frontier Science Program

**AWARD YEAR 1993 - Neuroscience Research Grants**

**McMahon** Andrew P.
Dept. of Cellular & Developmental Biology, Harvard University, Cambridge,
USA
**Ingham** Philip William
Dept. of Zoology, University of Oxford
UK
**Tabin** Clifford J.
Dept. of Genetics, Harvard University, Boston
USA
*Patterning of the mid-hindbrain region of the vertebrate embryo.*

# Cloning homologues of Drosophila hedgehog gene from the zebrafish

Stefan Krauss

Jean-Paul Concordet

C

```
hh       KRCKEKLNVLAYSVKEWPGIRLVVTEGWDEDYHHGQESLHYEGRAVTIATSDRDQSKYGMLAR
shh      QRCKDKLNSLAISVKEWPGVKLRVTEGWDEDGHHFEESLHYEGRAVDITTSDRDKSKYGTLSR
hh(a)    QRCKEKLNSLAISVKEWPGVKLRVTEGWDEDGNHFELSLHYEGRAVDITTSDRDRSKYGMFAR
hh(b)    QRCKDKLNSLAISVKNLWPGVKLRVTEGWDEDGLHSEESLHYEGRAVDITTSDRDRNKYRMLAR
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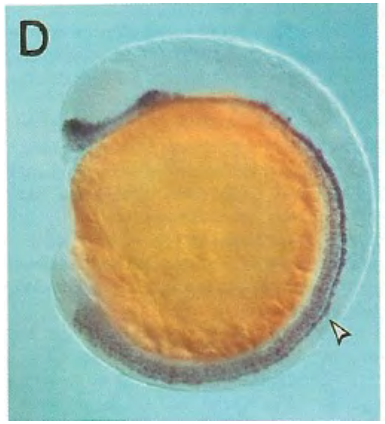
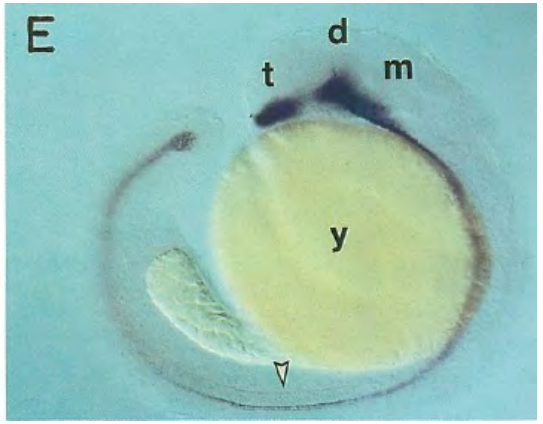
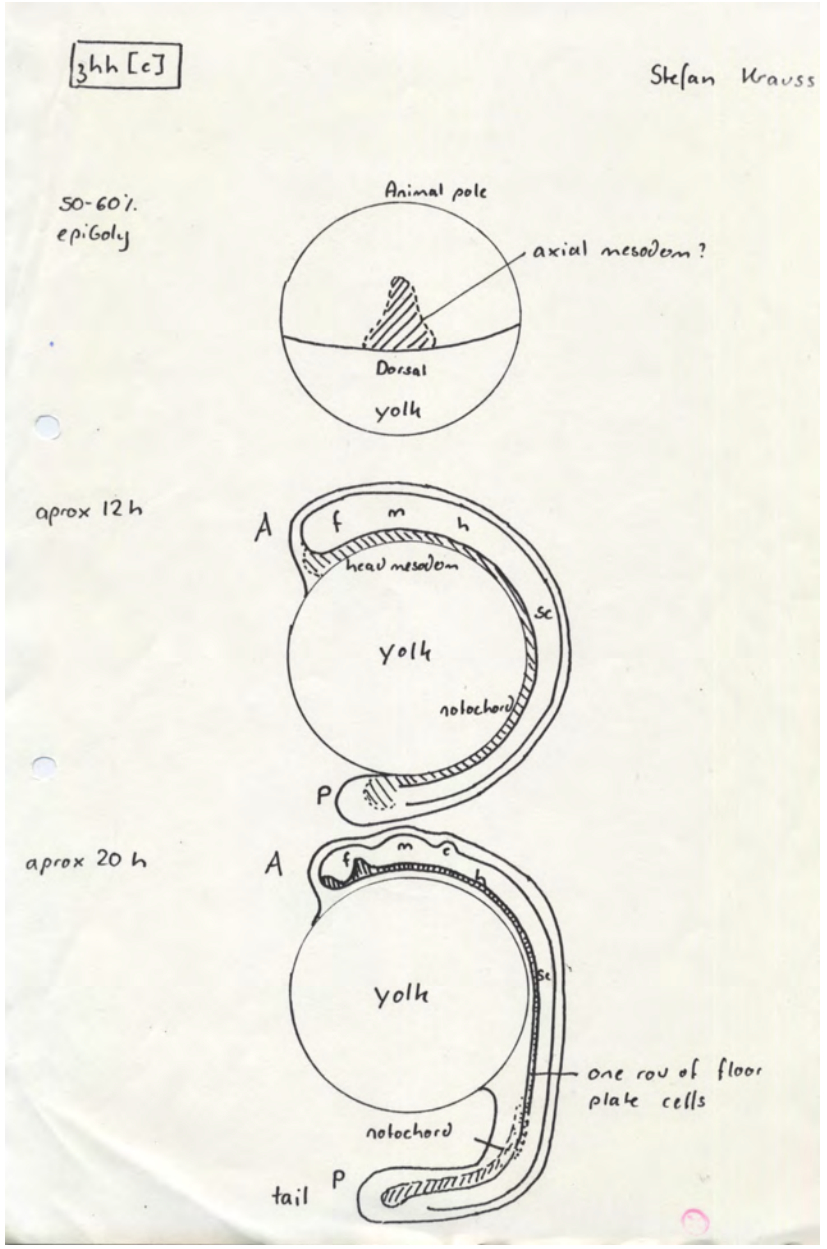


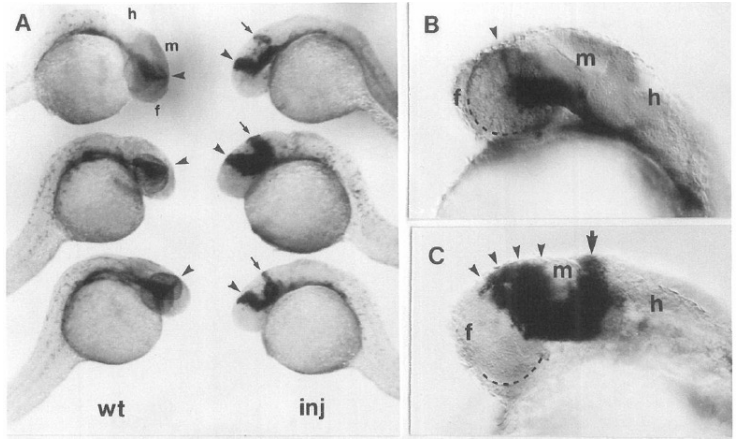



# Discovery of the vertebrate Hedgehog genes identifies their role as embryonic organisers


Cell, Vol. 75, 1431–1444, December 31, 1993, Copyright © 1993 by Cell Press

## A Functionally Conserved Homolog of the Drosophila Segment Polarity Gene *hh* Is Expressed in Tissues with Polarizing Activity in Zebrafish Embryos

S. Krauss, J.-P. Concordet, and P. W. Ingham




Cell, Vol. 75, 1401–1416, December 31, 1993, Copyright © 1993 by Cell Press

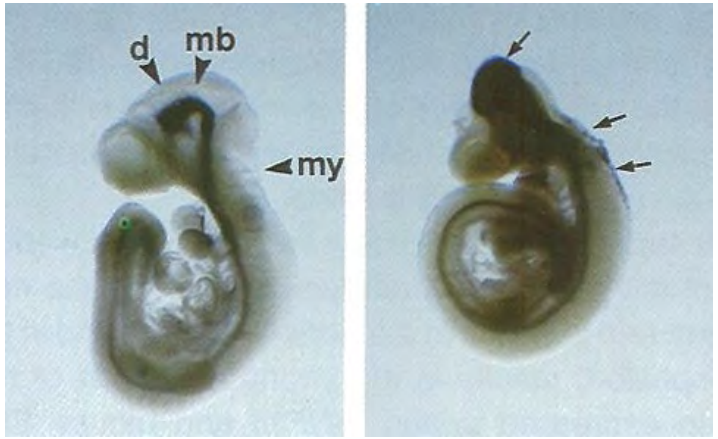
## *Sonic hedgehog* Mediates the Polarizing Activity of the ZPA

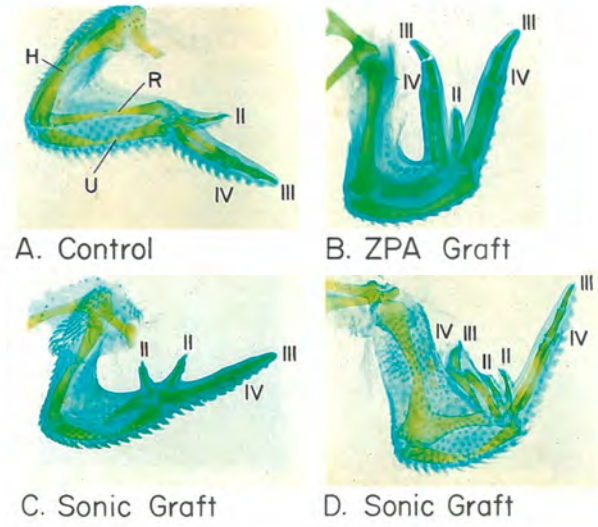
**Robert D. Riddle, Randy L. Johnson, Ed Laufer, and Cliff Tabin**
Department of Genetics
Harvard Medical School
Boston, Massachusetts 02115

Cell, Vol. 75, 1417–1430, December 31, 1993, Copyright © 1993 by Cell Press

## Sonic Hedgehog, a Member of a Family of Putative Signaling Molecules, Is Implicated in the Regulation of CNS Polarity

Yann Echelard,*§ Douglas J. Epstein,*§
Benoit St-Jacques,*§ Liya Shen,† Jym Mohler,‡
Jill A. McMahon,* and Andrew P. McMahon*



With the Arts
And Entertainment

**Science Times**

TUESDAY, JANUARY 11, 1994

The New York Times





# Biologists Find Key Genes That Shape Patterning of Embryos

By NATALIE ANGIER

A gene named hedgehog directs the development of cells in the limbs and brain.

RARE indeed are the scientific findings that make jaws drop and spirits do cartwheels. But the discovery of a class of genes, given the cheeky name hedgehog, has aroused the passions of developmental biologists so vigorously that their normal reserve and skepticism have dissolved, leaving them groping for ever-stronger ways to express the beauty and consequence of what has been divulged.

Three teams of scientists report in the current issue of the journal Cell that they have finally unearthed what developmental scientists have been seeking for the last 25 years, as they studied the implausibly complex sequence of events that allow a single cell, the fertilized egg, to efflloresce into a complete animal. They have identified the genes that act on the early embryo to lend it shape and pattern, transforming a nondescript comma of tissue into a vertebrate animal, with limbs and digits, brain and spinal cord, the body shape set from head to heel.

These genes produce so-called morphogens, molecules of celebrated stature that researchers have known must exist but have had tremendous difficulty isolating. The word morphogen means "maker of structure," and the hedgehog proteins are just that. Once switched on inside the embryo, the molecules sweep slowly across the primordial buds of tissue and begin generating identifiable form, sculpturing arms, hands and fingers on the sides of the embryo, vertebrae and ribs along its midline, a brain within the skull. The morphogen tells the cells it touches where they are situated in the body and what they are destined to become. It gives them their address, their fate, their identity, their purpose in life.

First detected in fruit flies, the hedgehog genes earned their name for their ability, when mutated, to give a fly the bristly appearance of a hedgehog. Their normal function in the fruit fly is to dictate growth, and the latest trio of reports establish that the same genes also dictate structural design in vertebrates.

The papers describe the isolation of hedgehog genes from mice, zebra fish and chickens, three staple organisms of laboratory research, widely separated in evolutionary time.

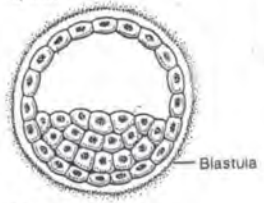
"This new class of signaling molecules will probably end up being the most important molecules in vertebrate development," said Dr. Clifford J. Tabin, a developmental biologist at Harvard Medical School and the principle author of one of the three reports. When the results on the hedgehog work first became apparent, he said, "I was bouncing off the walls."

Scientists have yet to look for the genes in humans, but they are certain that hedgehog is performing the same role in human embryos as it is in little fish. If this turns out not to be

Continued on Page C13

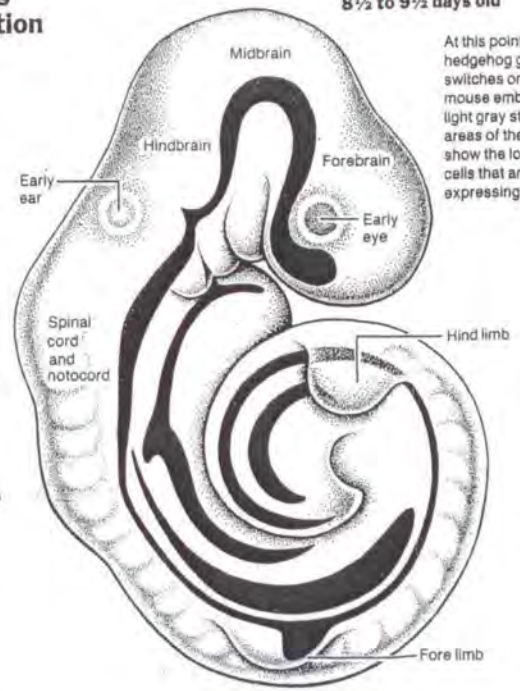
## A Gene That Signals Direction and Location

Scientists have discovered a class of genes, called hedgehog genes, that lend shape and pattern to the early embryo. Once turned on, these genes make proteins that give neighboring cells signals telling them their position and roles in forming a leg, wing or fin. At other sites, the hedgehog proteins direct development of the the central nervous system.



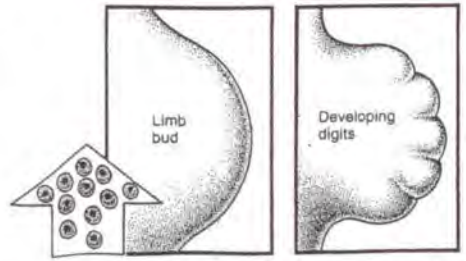

A fertilized mouse egg grows to be a cluster of 16 cells within three days. In the blastula stage, shown here, there are many more cells, and the inner cells have begun to take on specific roles.

**Mouse embryo, 8½ to 9½ days old**




At this point, the hedgehog gene switches on in the mouse embryo. The light gray stippled areas of the drawing show the locations of cells that are expressing this gene.

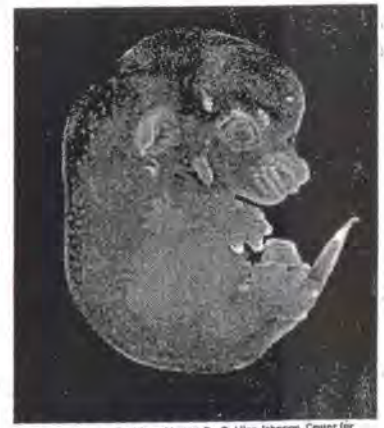
Within the early nervous system, the signals arising from the top and from the bottom are involved in formation of specific neurons at specific sites. Neurons at the top are associated with sensory functions, while neurons at the bottom control movement.




In the limb bud, the positional information from the hedgehog protein makes the cells start defining the arrangement of digits of a future paw.

Sources: Dr. Andrew McMahon, Harvard University; "Molecular Biology of the Cell" (Garland)

**Mouse embryo, 14 days old**



Dr. Bradley R. Smith, Dr. Elwood Lenny, Dr. G. Allan Johnson, Center for In Vivo Microscopy, Duke University Medical Center (N.I.H. National Resource)

Scientists suspect the hedgehog protein stimulates a master gene inside cells that sets off a cascade of other genes. The response to a signal, they think, depends on the local concentration of the hedgehog protein. Biologists expect to find the hedgehog gene in humans, too.

Nancy Sterngold, The New York Times; Illustration by Michael Reingold

Daily Post, Saturday, January 22, 1994

☐ Age-old puzzle solved by Crosby-born Philip Ingham

# Mersey scientists find key to life

# Su bl

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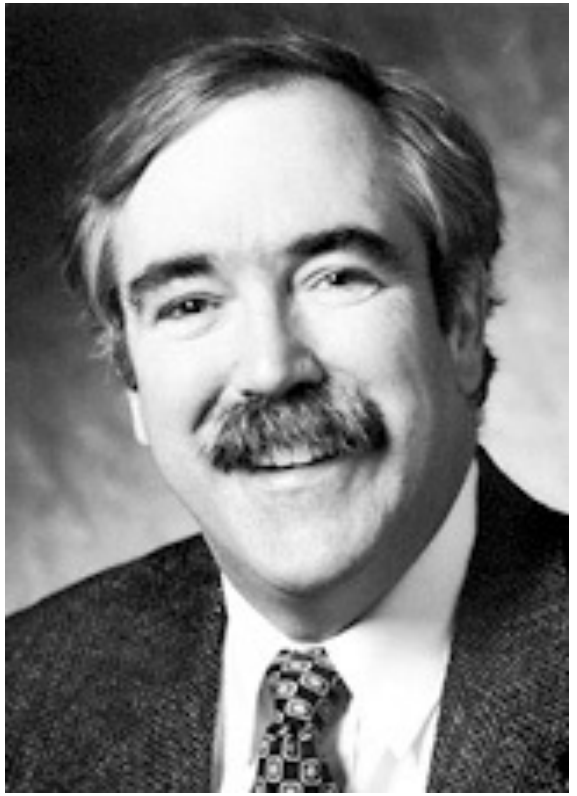
In 1995, the Nobel Prize in Physiology or Medicine was awarded jointly to Edward B. Lewis, Christiane Nüsslein-Volhard and Eric F. Wieschaus *"for their discoveries concerning the genetic control of early embryonic development"*.

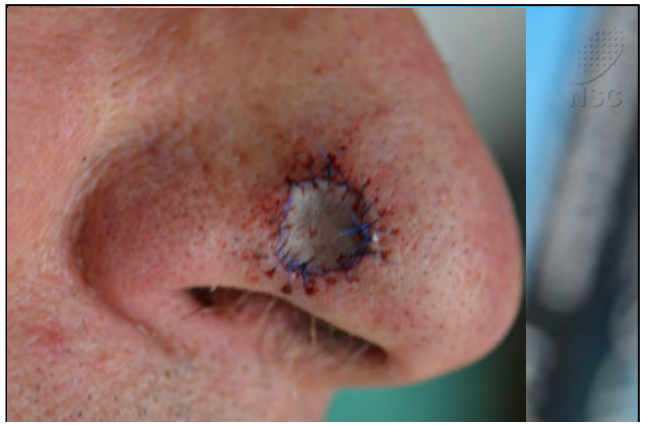


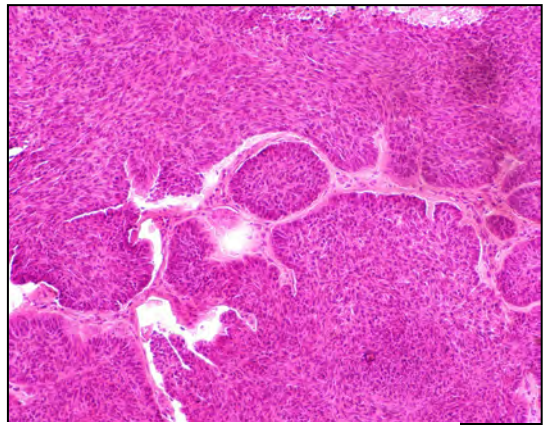
# The *Patched* gene is conserved in human and functions as a tumour suppressor

Cell, Vol. 85, 841–851, June 14, 1996, Copyright ©1996 by Cell Press

## Mutations of the Human Homolog of Drosophila *patched* in the Nevoid Basal Cell Carcinoma Syndrome

Heidi Hahn,[2,9] Carol Wicking,[1,9] Peter G. Zaphiropoulos,[5,9] Mae R. Gailani,[8] Susan Shanley,[7] Abirami Chidambaram,[3] Igor Vorechovsky,[5] Erika Holmberg,[5] Anne Birgitte Unden,[5,6] Susan Gillies,[1] Kylie Negus,[1] Ian Smyth,[1] Carolyn Pressman,[8] David J. Leffell,[8] Bernard Gerrard,[3] Alisa M. Goldstein,[4] Michael Dean,[2] Rune Toftgard,[5] Georgia Chenevix-Trench,[7] Brandon Wainwright,[1] and Allen E. Bale[8]





REPORT

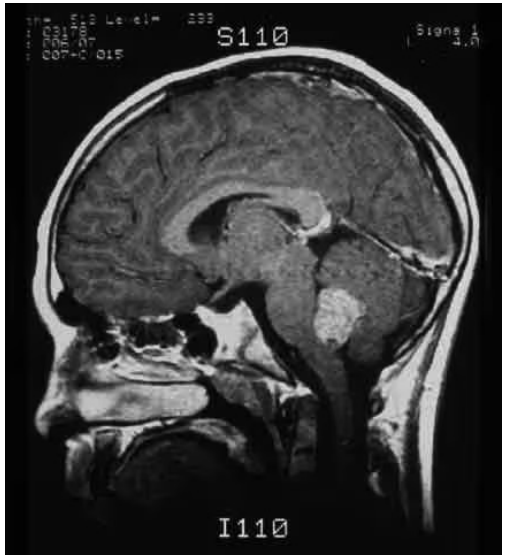
## Human Homolog of *patched*, a Candidate Gene for the Basal Cell Nevus Syndrome

Ronald L. Johnson, Alana L. Rothman, Jingwu Xie, Lisa V. Goodrich, John W. Bare, Jeannette M. Bonifas, Anthony G. Quinn*, Richard M. Myers, David R. Cox, Ervin H. Epstein Jr.†, Matthew P. Scott†

## Altered Neural Cell Fates and Medulloblastoma in Mouse *patched* Mutants

Lisa V. Goodrich, Ljiljana Milenković, Kay M. Higgins, Matthew P. Scott*

Oncogene (1997) 15, 361–366


## Somatic mutations in the human homologue of *Drosophila patched* in primitive neuroectodermal tumours

I Vořechovský[1,2], O Tingby[3], M Hartman[4], B Strömberg[5], M Nister[4], VP Collins[3] and R Toftgård[1]

# Identification of Smoothened as the obligate transducer of Hh signals

LETTERS TO NATURE

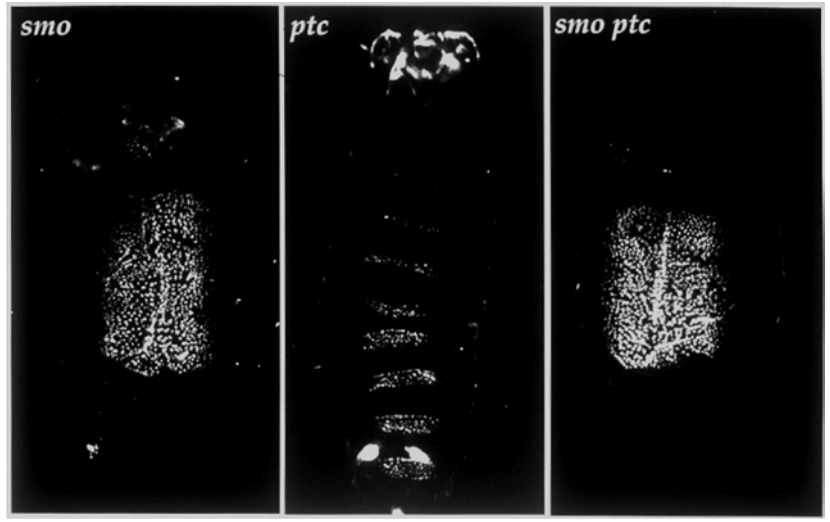
## *smoothened* encodes a receptor-like serpentine protein required for *hedgehog* signalling

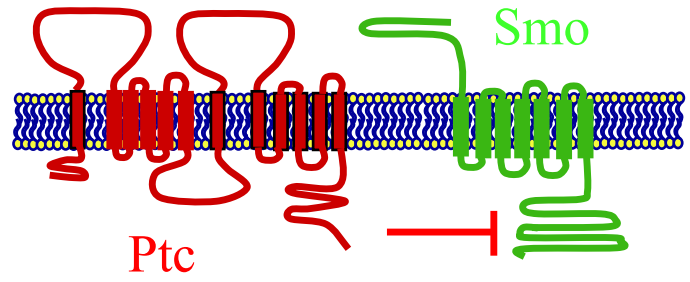
Marcel van den Heuvel & Philip W. Ingham

Molecular Embryology Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London WC2A 3PX, UK

MEMBERS of the Hedgehog family of secreted proteins control a number of important inductive interactions in the development of both vertebrates and *Drosophila*[1], but little is known about the ways in which their signalling activities are transduced. In *Drosophila*, *hedgehog* is one of the segment-polarity genes, mutations of which disrupt the pattern and polarity of individual embryonic segments[2] and their adult derivatives[3]; several of these genes have been implicated in transduction of the *hedgehog* signal[4–6]. Here we show that the segment-polarity gene *smoothened* is required for the response of cells to *hedgehog* signalling during the development of both the embryonic segments and imaginal discs. Sequence analysis of the *smoothened* transcription unit reveals a single open reading frame encoding a protein with seven putative transmembrane domains. This structure is typical of G-protein-coupled receptors, suggesting that the Smoothened protein may act as a receptor for the Hedgehog ligand.

NATURE · VOL 382 · 8 AUGUST 1996




letters to nature

## Activating *Smoothened* mutations in sporadic basal-cell carcinoma

**Jingwu Xie*, Maximilien Murone†, Shiuh-Ming Luoh†, Anne Ryan‡, Qimin Gu§, Chaohui Zhang†, Jeannette M. Bonifas*, Ching-Wan Lam‖, Mary Hynes¶, Audrey Goddard§, Arnon Rosenthal¶, Ervin H. Epstein Jr* & Frederic J. de Sauvage†**

** Department of Dermatology, San Francisco General Hospital, 1001 Potrero Street, Rm 269, Bldg 100, University of California, San Francisco, California 94110, USA*

*Departments of † Molecular Oncology, ‡ Pathology and § Molecular Biology and ¶ Neuroscience, Genentech Inc., 1 DNA Way, South San Francisco, California 94080, USA*

*‖ Department of Chemical Pathology, Prince of Wales Hospital, Shatin, Hong Kong*

NATURE | VOL 391 | 1 JANUARY 1998

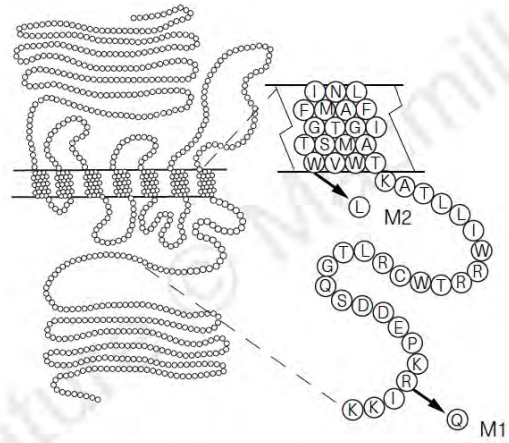



**Figure 3** Predicted structure of the human SMO protein[8].The location of two mutations identified in three BCC sporadic tumours is indicated. The mutation Trp 535 to Leu in the seventh transmembrane domain was identified in two separate tumours (M2). One mutation, Arg 562 to Gln, was identified in the carboxy-terminal cytoplasmic tail of SMO (M1).

# Patenting of Hedgehog signalling

## Vertebrate embryonic pattern-inducing proteins and uses related thereto

**Document Type and Number:** United States Patent 6607913

**Abstract:**
The present invention concerns the discovery that proteins encoded by a family of vertebrate genes, termed here hedgehog-related genes, comprise morphogenic signals produced by embryonic patterning centers, and are involved in the formation of ordered spatial arrangements of differentiated tissues in vertebrates. The present invention makes available compositions and methods that can be utilized, for example to generate and/or maintain an array of different vertebrate tissue both in vitro and in vivo.

**Inventors:** Ingham, Philip W. (Summertown, Oxford OX27L, GB)
Mcmahon, Andrew P. (Lexington, MA)
Tabin, Clifford J. (Cambridge, MA)

**Application Number:** 09/448188
**Publication Date:** 08/19/2003
**Filing Date:** 11/23/1999

This IP provided the foundation for a new biotech start-up established by Doug Melton (Harvard University)

Ontogeny, Inc.

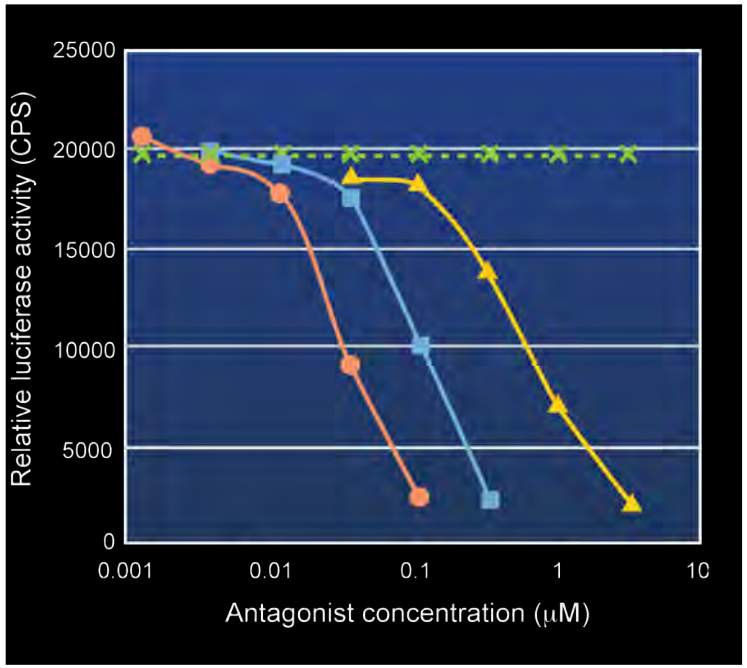
# *Drosophila* studies provided the basis of screens for small molecule modulators of Hh

GENES & DEVELOPMENT 10:2003–2013 © 1996 by Cold Spring Harbor Laboratory Press ISSN 0890-9369/96 $5.00 2003

**Transcriptional activation of *hedgehog* target genes in *Drosophila* is mediated directly by the Cubitus interruptus protein, a member of the GLI family of zinc finger DNA-binding proteins**

Cyrille Alexandre, Antonio Jacinto, and Philip W. Ingham[1]

Molecular Embryology Laboratory, Imperial Cancer Research Fund, London, WC2A 3PX, United Kingdom




*Ontogeny Inc.* begin screens of synthetic small molecules for anti-Hh activity using a Gli-reporter-gene-based assay in tissue culture cells.

The company merges with two other start-ups to form

CURIS™

J. Biol. Journal of Biology

BioMed Central

Research article

**Small-molecule modulators of Hedgehog signaling: identification and characterization of Smoothened agonists and antagonists**

Maria Frank-Kamenetsky*, Xiaoyan M Zhang*, Steve Bottega*, Oivin Guicherit*, Hynek Wichterle†, Henryk Dudek*, David Bumcrot*, Frank Y Wang*, Simon Jones*, Janine Shulok*, Lee L Rubin* and Jeffery A Porter*

Addresses: *Curis, Inc., 61 Moulton Street, Cambridge, MA 02138, USA. †Columbia University, College of Physicians and Surgeons, 701 West 168 Street, New York, NY 10032, USA.

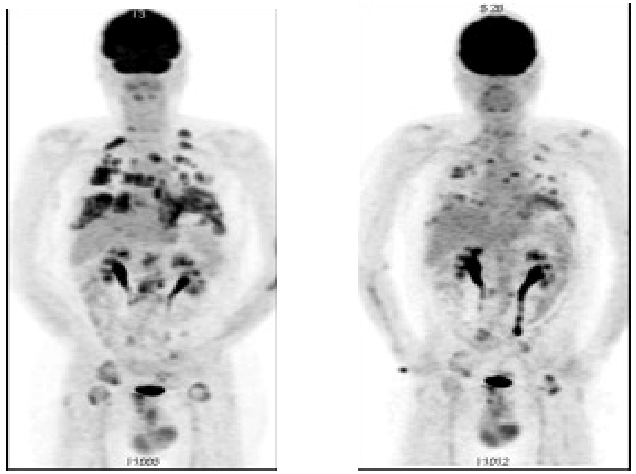
# Vismodegib: first precision therapy for metastatic basal cell carcinoma

The NEW ENGLAND JOURNAL of MEDICINE

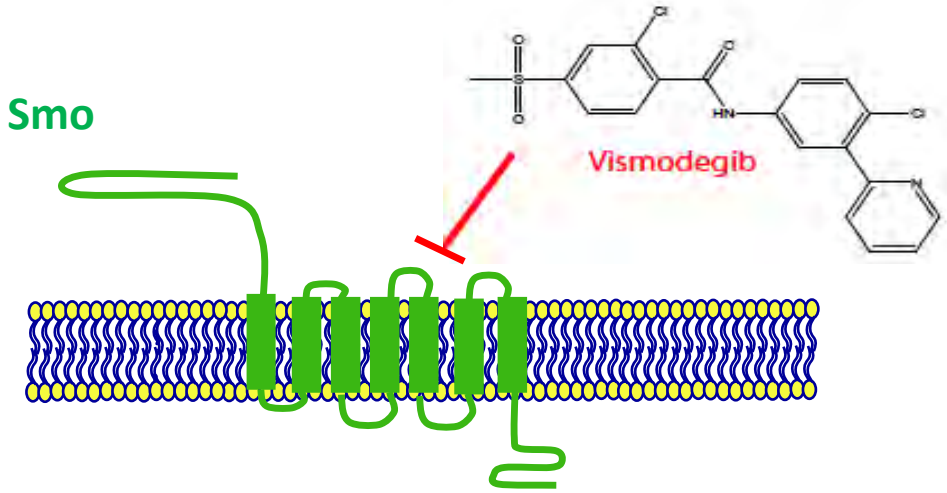
ORIGINAL ARTICLE

## Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma

Daniel D. Von Hoff, M.D., Patricia M. LoRusso, D.O., Charles M. Rudin, M.D., Ph.D., Josina C. Reddy, M.D., Ph.D., Robert L. Yauch, Ph.D., Raoul Tibes, M.D., Glen J. Weiss, M.D., Mitesh J. Borad, M.D., Christine L. Hann, M.D., Ph.D., Julie R. Brahmer, M.D., Howard M. Mackey, Ph.D., Bertram L. Lum, Pharm.D., Walter C. Darbonne, M.S., James C. Marsters, Jr., Ph.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.



N ENGL J MED 361;12 NEJM.ORG SEPTEMBER 17, 2009

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Cancer Drug Information

**Posted:** 01/30/2012

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- NCI Drug Dictionary
- Search for Clinical Trials

### FDA Approval for Vismodegib

**Brand name: Erivedge®**

- To treat metastatic or recurrent locally advanced basal cell carcinoma in adults who cannot be treated with surgery or radiation

Full prescribing information is available, including clinical trial information, safety, dosing, drug-drug interactions, and contraindications.

On January 30, 2012, the Food and Drug Administration (FDA) approved vismodegib (Erivedge® Capsule, made by Genentech, Inc.) for the treatment of adults with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

**Related Pages**
- Skin Cancer Home Page
- Chemotherapy and You: Support for People With Cancer
- Chemotherapy Side Effects Fact Sheets
- Cancer Drug Information

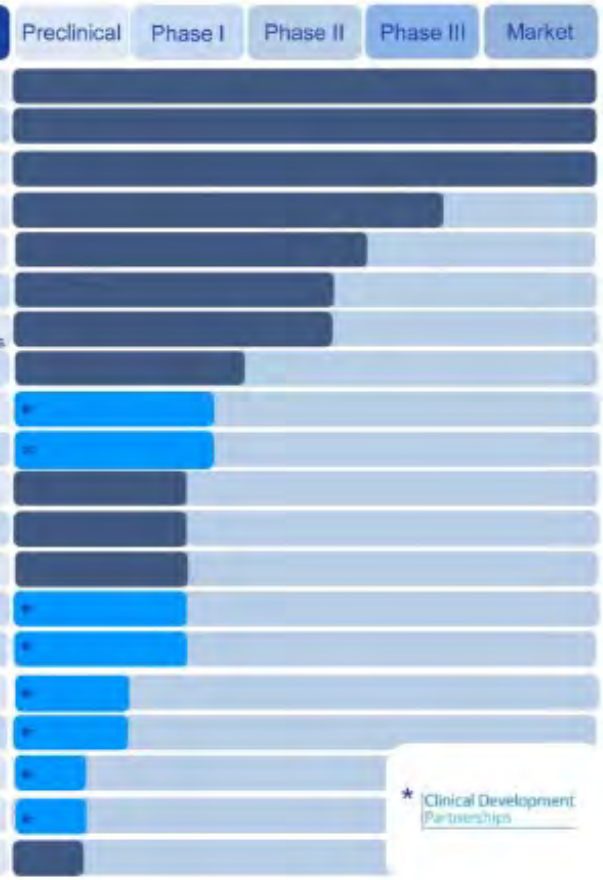
News

# Drug Discovery of the Year awarded to team behind vismodegib

Rick Graham, Clinical Pharmacologist and acting Global Development Leader for vismodegib at Genentech, commented, "We are very proud that our understanding of the Hedgehog signalling pathway enabled us to develop a medicine which today is providing meaningful benefit to patients with advanced basal cell carcinoma."

# Selected Partnered Therapeutics in Development

| Agent/Target | Company | Institute | Indications |
|---|---|---|---|
| Temodal® | Schering-Plough (now Merck) | Aston | Glioma |
| Zytiga® | Cougar (now J&J); BTG | ICR | Prostate |
| Erivedge™ | Genentech/Roche; Curis | Harvard; CRT | BCC |
| Anyara | Active Biotech | PICR | Renal |
| TG4010 | Transgene | Guy's Hospital | Non small cell lung cancer |
| HSP90 | Novartis; Vernalis | ICR | NSCLC; Breast |
| SG 2000 | Spirogen | Portsmouth; London School of Pharmacy | Ovarian; Haematological tumours |
| PARP | Pfizer; AstraZeneca | Newcastle; ICR; Sheffield | Ovarian; Breast; Melanoma |
| GSK1070916A | GSK | | Advanced solid tumours |
| IMA950 | Immatics biotechnologies | | Glioblastoma Multiforme |
| PI 3-kinase | Genentech; Piramed | LRI; ICR; Ludwig | |
| ONX-0801 | Onyx Pharmaceuticals | ICR | Advanced solid tumours |
| Akt/PKB | AstraZeneca; Astex | ICR | |
| AT 13148 | Astex Therapeutics | | Advanced solid tumours |
| AZD 0424 | AstraZeneca | | Advanced solid tumours |
| AZD 3965 | AstraZeneca | | |
| DI-B4 | Merck KGaA | | Leukaemia & Lymphoma |
| CEN-209 | Auckland Uniservices | | Advanced solid tumours |
| IL17E | Lorus Therapeutics | | |
| Undisclosed | Genentech | Oxford | |




CRT has >30 partnered agents in preclinical and clinical development and 3 partnered marketed drugs

Cancer Research Technology

Advancing Discoveries to Beat Cancer

# The story of vismodegib and skin cancer

Category: Science blog | June 7, 2012 | Safia Danovi | 3 comments | 8 minute read

This entry is part 11 of 30 in the series Our milestones

The course of drug development never did run smooth. Drug development pipelines – like the X-Factor – are littered with thousands of 'hopefuls' who fail to make the cut.

Very few drugs survive the arduous journey from bench to bedside, and those that do often emerge ten to twenty years later, bearing little resemblance to their former selves.

In fact, only about one in ten drugs initially tested in patients make it through to routine use. So it's always good news when an experimental drug makes it all the way through the difficult journey of tests and clinical trials.

As we reported in 2012, vismodegib (Erivedge) – a skin cancer drug that our work helped shape – was described as "the greatest advance in therapy yet seen for this disease" in the prestigious *New England Journal of Medicine*. And in 2013, the drug was approved by the European Medicines Agency and will be available in England for NHS patients through the Cancer Drugs Fund.

So in the latest of Our Milestones series, we'd like to tell the story of Professor Phil Ingham, and how his fundamental research in fruit flies and fish evolved into a drug that could revolutionise treatment for patients with advanced basal cell carcinoma – a type of skin cancer.

Professor Phil Ingham, whose Cancer Research UK-funded work in the 1990s has led to vismodegib, a new skin cancer drug

## Molecular GPS

# Hedgehog signalling is now implicated in a host of clinical conditions

nature communications

Article

https://doi.org/10.1038/s41467-022-32229-9

## Primary cilia and SHH signaling impairments in human and mouse models of Parkinson's disease

Received: 3 August 2021

Accepted: 21 July 2022

Published online: 16 August 2022

Check for updates

Sebastian Schmidt[1,2,16], Malte D. Luecken[3,16], Dietrich Trümbach[1,4,16], Sina Hembach[1,2], Kristina M. Niedermeier[1,2], Nicole Wenck[1,2], Klaus Pflügler[1,2], Constantin Stautner[1,2], Anika Böttcher[5], Heiko Lickert[5], Ciro Ramirez-Suastegui[3], Ruhel Ahmad[6], Michael J. Ziller[7], Julia C. Fitzgerald[8], Viktoria Ruf[9,10], Wilma D. J. van de Berg[11], Allert J. Jonker[11], Thomas Gasser[8], Beate Winner[12], Jürgen Winkler[13], Daniela M. Vogt Weisenhorn[1,2], Florian Giesert[1] ✉, Fabian J. Theis[3,14] ✉ & Wolfgang Wurst[1,2,10,15] ✉

Journal of the American Heart Association

ORIGINAL RESEARCH

## Intact Fibroblast Growth Factor 23 Regulates Chronic Kidney Disease–Induced Myocardial Fibrosis by Activating the Sonic Hedgehog Signaling Pathway

Lanlan Li, MM; Hua Gan, MD

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

## Inhibition of GPR39 restores defects in endothelial cell–mediated neovascularization under the duress of chronic hyperglycemia: Evidence for regulatory roles of the sonic hedgehog signaling axis

Sai Pranathi Meda Venkata[a], Hainan Li[a], Liping Xu[a], Jia Yi Koh[a], Huong Nguyen[a], Morgan Minjares[a], Chunying Li[b], Anjaneyulu Kowluru[a,c], Graeme Milligan[d], and Jie-Mei Wang[a,e,1]

Edited by Napoleone Ferrara, University of California San Diego, La Jolla, CA; received May 19, 2022; accepted November 21, 2022

Received: 27 October 2021 | Revised: 24 March 2022 | Accepted: 27 March 2022

DOI: 10.1111/jnc.15613

Journal of Neurochemistry JNC WILEY

ORIGINAL ARTICLE

## Hedgehog signaling plays a crucial role in hyperalgesia associated with neuropathic pain in mice

Hiroaki Okuda | Tatsuya Ishikawa | Kiyomi Hori | Nichakarn Kwankaew | Noriyuki Ozaki

Full length article

## Sonic hedgehog delivery from self-assembled nanofiber hydrogels reduces the fibrotic response in models of erectile dysfunction ☆

Shawn Choe[a], Dorina Veliceasa[a], Christopher W. Bond[b], Daniel A. Harrington[c], Samuel I. Stupp[d,e,f,g], Kevin T. McVary[h], Carol A. Podlasek[a,i,*]

[a] Department of Urology, University of Illinois at Chicago, Chicago, IL 60612, United States
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[i] Department of Physiology and Bioengineering, University of Illinois at Chicago, Chicago, IL 60612, United States

# Notable Ingham Research Laboratory Alumni

**PhD STUDENTS**

| | |
|---|---|
| Alicia Hidalgo | Professor of Neurogenetics, University of Birmingham, UK |
| Alexandria Forbes | Founder, President and CEO, MeiraGTx, New York, USA |
| Patrick Blader | INSERM Director, Montpellier, France |
| Antonio Jacinto | Director, Institute for Chronic Disease Research, Lisbon, Portugal |
| Kate Lewis | Professor and Head of Department, State University of New York, Stonybrook, USA |
| Anish Shivdasani | Founder and President, Giraffe, Johannesburg, South Africa |

**POSTDOCTORAL FELLOWS**

| | |
|---|---|
| Isabel Guerrero | Principal Scientist, Universidad Autonoma, Madrid |
| Yoshiro Nakano | Senior Scientist, Hyogo University Medical School, Japan |
| Uwe Strähle | Director, Centre for Toxicology, Karlsruhe, Germany |
| Stefan Krauss | Director, HTH Centre of Excellence, University of Oslo, Norway |
| Jean-Paul Concordet | Research Director, INSERM, Paris, France |
| Tom Schilling | Head of Department Biology, UC Irvine, California, USA |
| Pete Currie | Director, Australian Regenerative Medicine Institute, Monash, Australia |
| Sudipto Roy | Principal Scientist, IMCB, Singapore |
| Leanne Jones | Director, Bakar Aging Research Institute, UCSF, California, USA |

# Research with Impact

in the new Department of Life Sciences

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News story

# Chancellor reveals life sciences growth package to fire up economy

A £650 million war-chest to fire up the UK's life sciences sector and drive forward the government's priority to grow the economy has been unveiled by the Chancellor of the Exchequer Jeremy Hunt today 25 May 2023.

***Life Sciences is one of the UK's most successful sectors, worth over £94 billion to the UK economy in 2021, a 9% increase on the year before.***

The multi-faceted 'Life Sci for Growth' package brings together 10 different policies including:

•£121m to improve commercial clinical trials to bring new medicines to patients faster

• up to £48m to support development of manufacturing processes for next-generation vaccines and advanced therapies

• £52.7m to support new mental health treatments, set up new research centres and develop new treatments for addiction

• £31m for the Life Sciences Innovative Manufacturing Fund

•£154m for upgrading the UK Biobank to meet increasing demand for this world leading biomedical research database

# Weatherwatch: climate crisis causing tropical viruses to spread

Infections such as dengue fever on rise in Europe as virus-transmitting mosquitoes expand habitats

Dengue, a disease transmitted by mosquitoes, has been spreading to an unprecedented level in France. Photograph: Manjunath Kiran/AFP/Getty Images

# Global pollinator losses causing 500,000 early deaths a year – study

**Insect declines mean reduced yields of healthy foods like fruit and vegetables and increased disease in people**

A bee sits on a flower budding from an almond tree. Three-quarters of crops require pollination. Photograph: Amir Cohen/Reuters

# Drugs have dangerously polluted the world's rivers, scientists warn

**Pharmaceutical pollution poses 'global threat to human and environmental health', major study finds**

The Kai Tak river in Hong Kong had 34 different active pharmaceutical ingredients at a single site, the highest number recorded. Photograph: Robert Harding/Rex/Shutterstock

# Climate crisis inflicting huge 'hidden costs' on mental health

**Vicious circle of climate impacts, trauma and depression must be broken, say scientists**

A man walks through a flooded street caused by Hurricane Eta in Planeta, Honduras, in 2020.

# World's food supply under 'severe threat' from loss of biodiversity

**Plants, insects and organisms crucial to food production in steep decline, says UN**

Organic carrot harvest in Germany. Organic agriculture makes up just 1% of global farmland.

# Air pollution raises risk of type 2 diabetes, says landmark Indian study

**Seven-year study of 12,000 residents of Delhi and Chennai finds link between PM2.5 particles and increased blood sugar levels**

People walk on a road towards the India Gate amid smog in New Delhi. India is one of the


World Health Organization

**One Health** is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems.

It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent.

# Protecting ecosystems: Ecology and Conservation

Insect control

pollinators

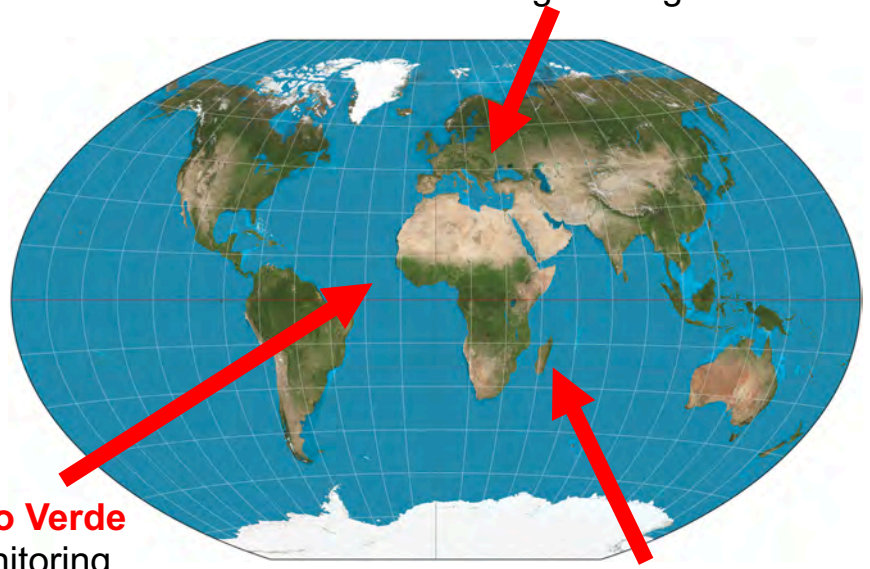
Seed dispersal and reforestation

**Emma Stone**

**Tamas Szekely**

- Assessing population level impacts of urbanisation and lighting on bats in the UK and Africa
- Using socio-cultural-ecological approaches to understand human wildlife conflict (HWC) in urban areas
- Working with Natural England and North Somerset Council – informing national planning policy and bat species legislation
- Creating national guidance for lighting industry for bats and lighting (ILP, TRT Lighting Ltd)
- Improved wellbeing for communities living with bats through mitigation of HWC

**Hungary**
Restoring grasslands for insects and birds
Protecting nesting birds



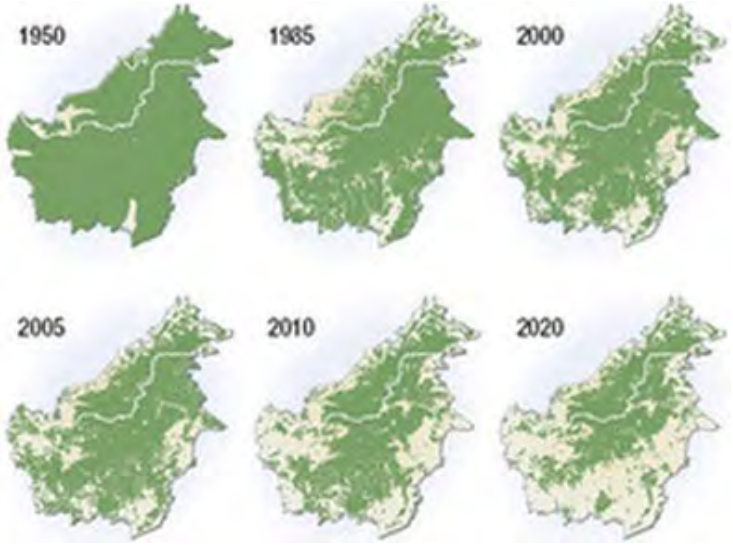
**Cabo Verde**
Monitoring endangered birds
Founded conservation NGO

**Madagascar**
Monitoring endangered birds

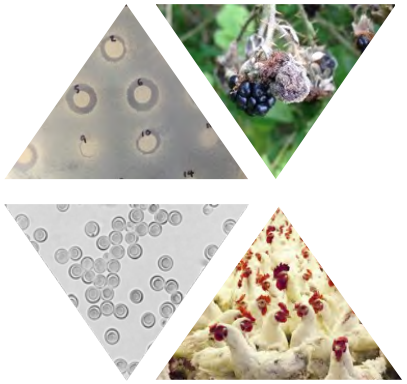
Source: Bat Conservation Trust

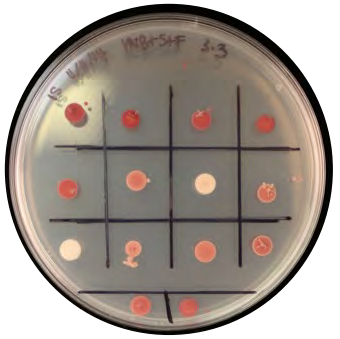
# Sustainable Alternatives to Palm Oil: adaptive evolution

orangutanfoundation.org




Treehugger.com





*Metschnikowia pulcherrima* (Mp) – naturally occurring environmental yeast

- Accumulates lipids with good chemical profiles (e.g. Palm-like)

Adaptive laboratory evolution nearly doubled lipid yield to above 40%

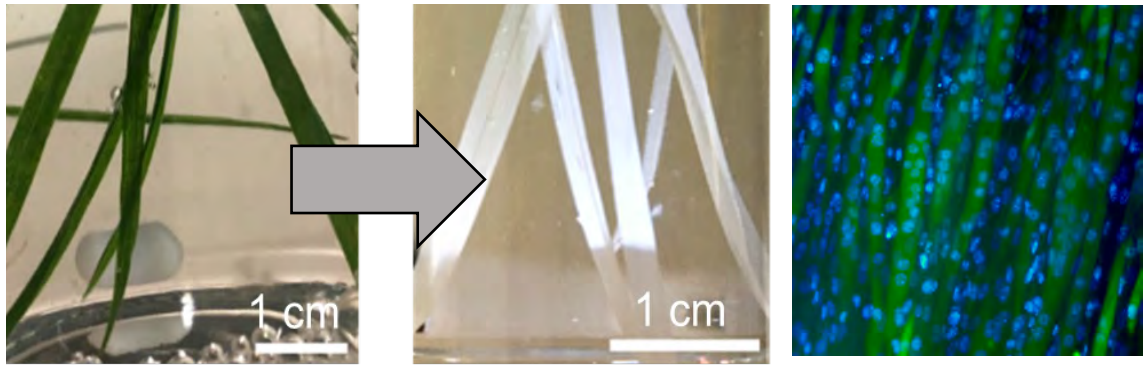
Successful scale-up for industry

**Chris Chuck** – Dept of Chemical Engineering

**Daniel Henk**

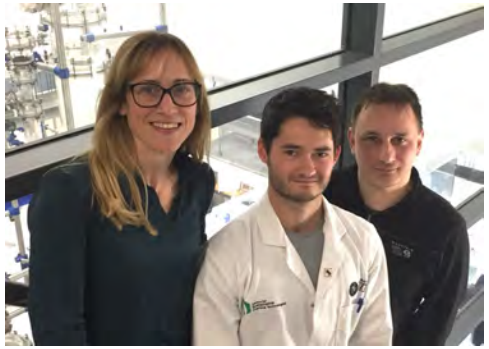
# Sustainable Alternatives to meat production: cultured muscle


The Guardian June 2023




Paul de Bank (Dept Life Sciences)

Marianne Ellis (Dept Chem. Engineering)



- Cultured meat has the potential for a massive reduction in the climate impact of industrial farming
- take muscle cell samples from livestock and grow them on a large scale
- Challenge: how can the aligned muscle fibres found in natural meat be replicated in culture?
- Solution: grow cultured muscle cells on a scaffold that provides suitable physical guidance
- Challenge: scaffold needs to be renewable and edible to enable scalable culture
- Solution: decellularized grass

# Exploiting evolutionary genetics to control pesticide resistance

**Jason Wolf**

The time it takes for resistance emergence is a key determinant of *pesticide sustainability*

- Develop optimal pest control strategies by combing evolutionary genetics theory and computational genomics

**Phil Madgwick**

syngenta

<u>Sustainable agriculture</u>

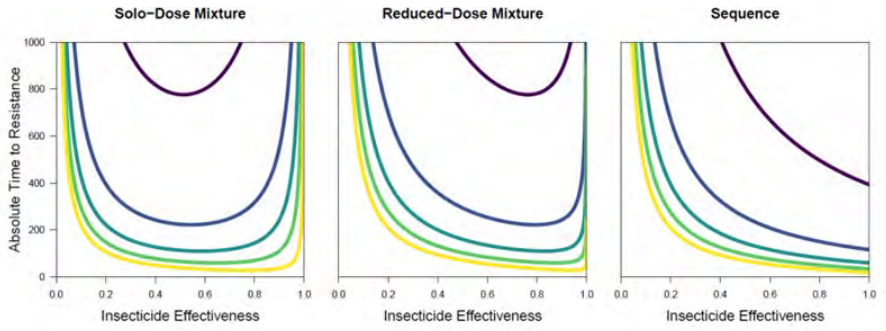
Prevent pest control failure

<u>Global health</u>

Malaria control

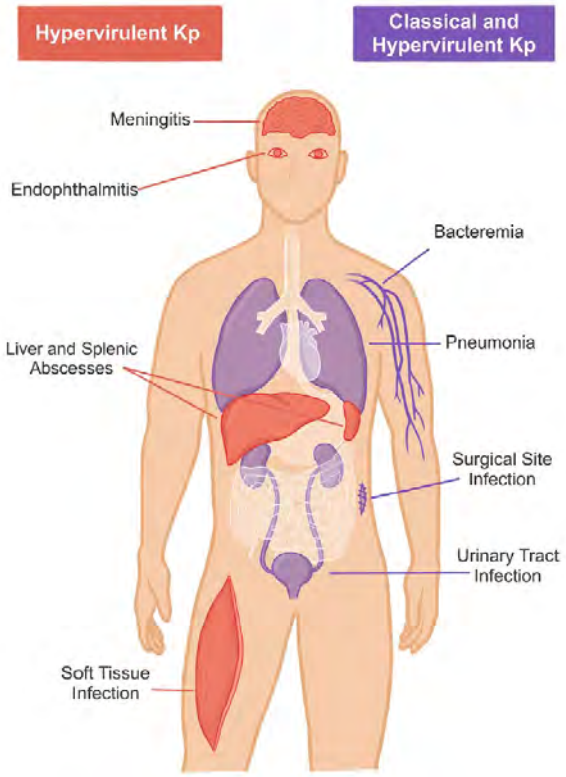
BILL & MELINDA GATES foundation

$$T_{mix} = \frac{\log\left(\frac{f_{A,T}(1-f_{A,0})}{(1-f_{A,T})}\right)}{\log\left(\frac{\sqrt{1-m}}{1-m}\right)}$$



# Tracking evolution and spread of antibiotic resistance

**Ed Feil**




Gozalez-Ferrer et al (2021) Infection & Immunity

- use genomics to understand and manage the spread of **antibiotic resistant** bacterial pathogens of humans and animals.

nature microbiology

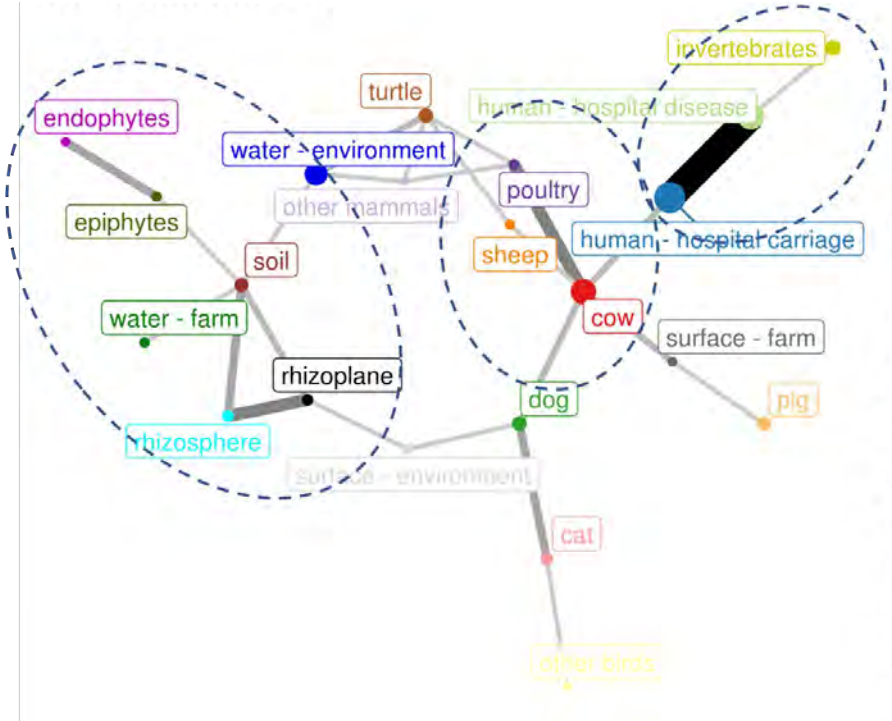
Article

https://doi.org/10.1038/s41564-022-01263-0

**A large-scale genomic snapshot of *Klebsiella* spp. isolates in Northern Italy reveals limited transmission between clinical and non-clinical settings**

- focus on non-clinical ('One-Health') settings, in both high-and low-income countries

- ongoing project understanding the diversity and spread *of E. coli* and *Klebsiella* plasmids

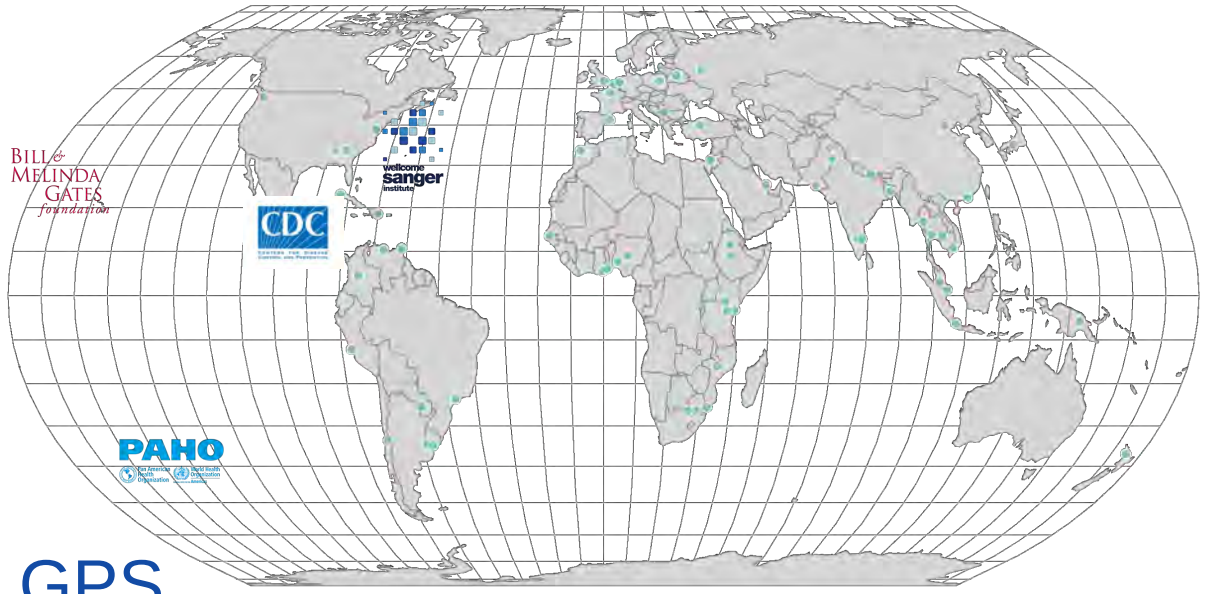


# Global genomic surveillance to understand vaccine impact

**Stephanie Lo**

***Streptococcus pneumoniae***

- Leading cause of community acquired pneumonia and meningitis in young children
- Pneumococcal conjugate vaccine
- Vaccine escape due to expansion of preexisting strains and novel recombinants




- Largest genome project of a single bacterial species (>26,000 genomes across 60 countries)
- Established a genomic definition of pneumococcal lineages
- **Identified pneumococcal lineages mediate vaccine escape** at global and country level
- **First exemplar** to use genomic surveillance finding to guide inclusion of serotype 24F in the upcoming 25-valent pneumococcal conjugate vaccine

GPS

The Global Pneumococcal Sequencing project

# Vaccine epidemiology using real-world data


**The World Health Organization (WHO) has identified vaccine hesitancy as one of the biggest threats to global health.**

**Helen McDonald**

**Vaccine safety and effectiveness**

(e.g. shingles, maternal pertussis and influenza, and COVID-19 vaccines)

| **Vaccine access and inequalities in coverage** | **Methodology** for using real-world data and addressing bias |
|---|---|

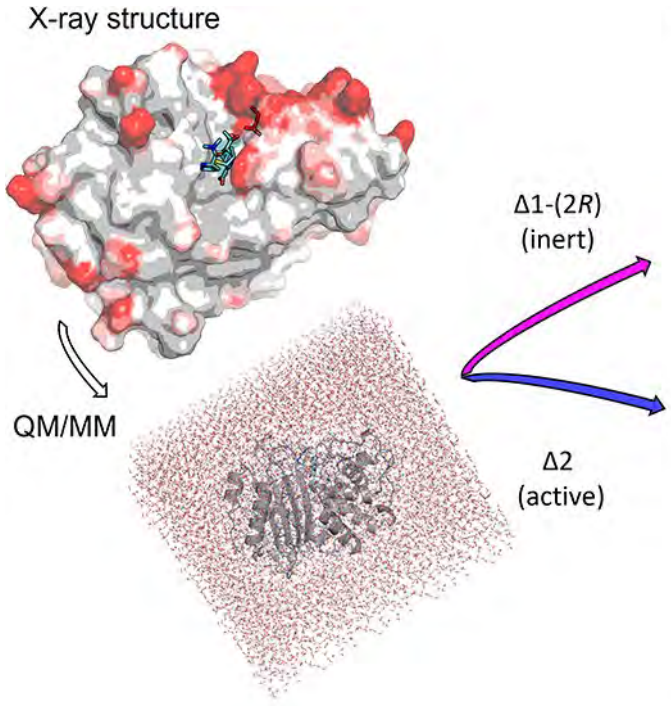
**Research with impact: COVID-19 vaccine prioritisation**

- Led and collaborated on studies of factors associated with COVID-19 mortality
- Briefed the JCVI on UK COVID-19 vaccine prioritisation, supporting an age-based approach and definition of high-risk groups (Dec 2020)
- Co-led research on risk of severe COVID-19 for people with learning disability
- COVID-19 vaccine prioritised to everyone on the learning disability register in the UK (Feb 2021)

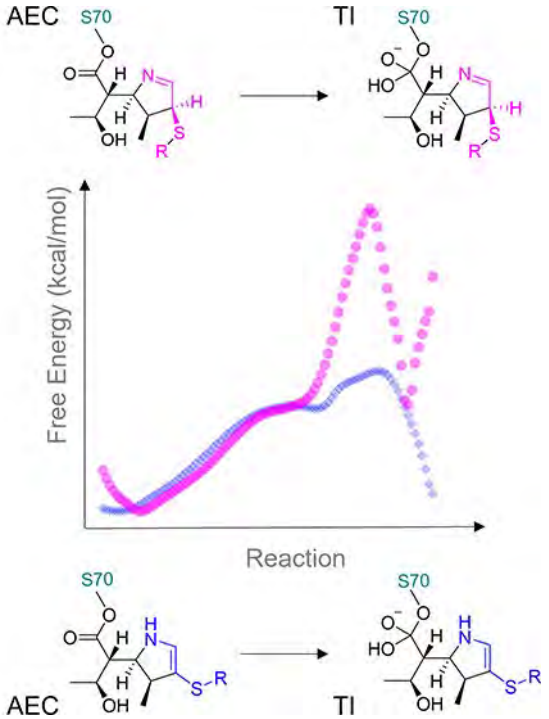
**Catherine Tooke**

# Antibiotic action and resistance in Gram-negative bacteria

Gram-negative bacteria cause a range of infections in healthcare settings, such as pneumonia, bloodstream infections, wound/surgical site infections and meningitis. They are increasingly resistant to most available antibiotics, including β-lactams (eg. Penicillins)




Hybrid Quantum Mechanics/ Molecular Mechanics simulations

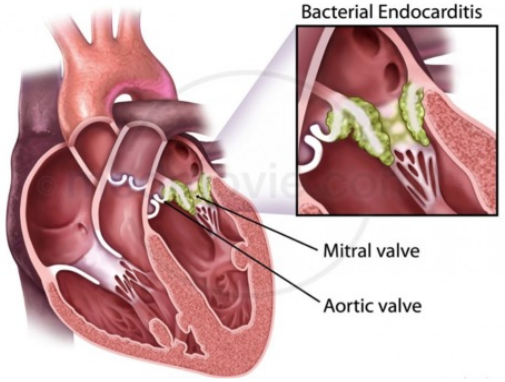



Identification of activity/inhibition determinants

Catherine takes an integrated approach of microbiology, biochemistry, protein structure and biomolecular simulation to investigate the key factors that govern β-lactam binding, activity and mechanism within targets (penicillin binding proteins) and resistance enzymes (β-lactamases).

The detailed mechanistic understanding can inform new strategies to combat β-lactam failure.

# Overcoming Antibiotic Resistance using Covalent Macrocycles

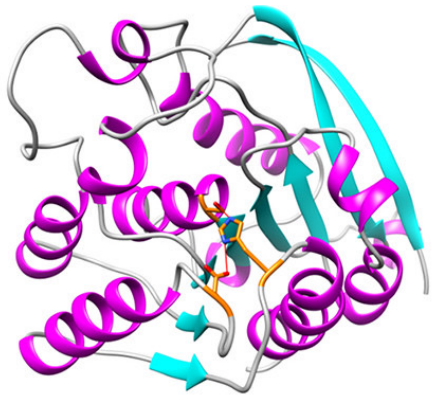



Staphylococcus aureus infections

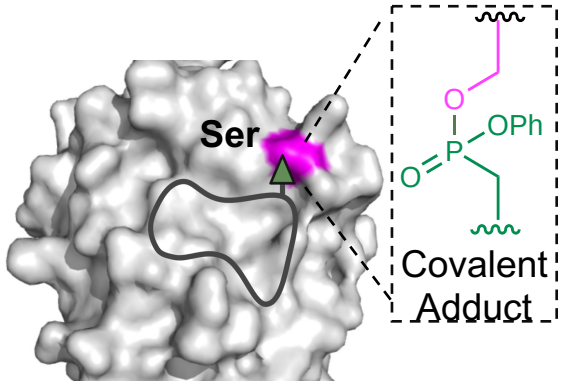
- FphF is a serine hydrolase virulence factor expressed on the surface of *S. aureus* cells. Its role in infection and its accessibility make it an excellent drug target
- Covalent macrocycles can act as potent inhibitors of individual protease targets with minimal off-target toxicity
- Screening a billion-member covalent macrocycle libraries has yielded a highly specific nanomolar inhibitor of FphF

**Scott Lovell**

***S. aureus* is the primary cause of infective endocarditis. New tools to treat antibiotic-resistant endocarditis infections are urgently needed.**

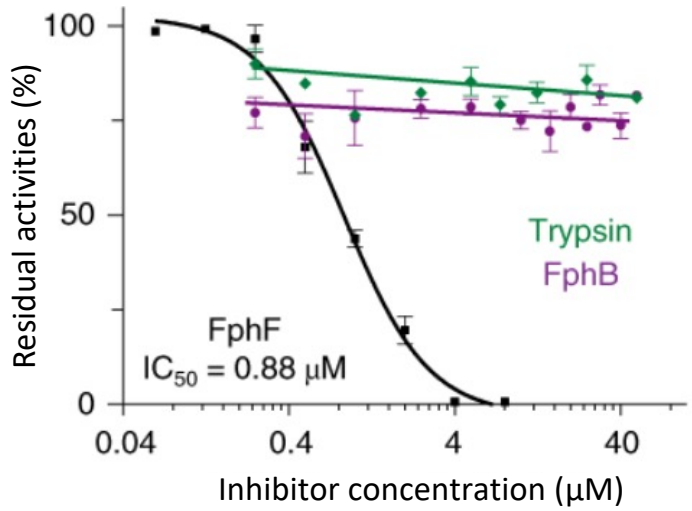


FphF – a serine hydrolase virulence factor




Electrophile — Macrocycle

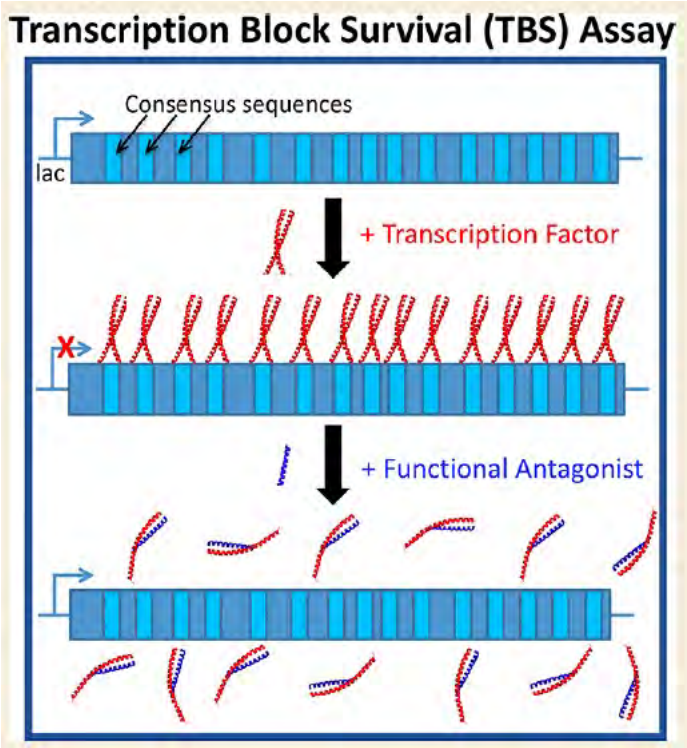
Catalytic Serine Residue



Jody Mason

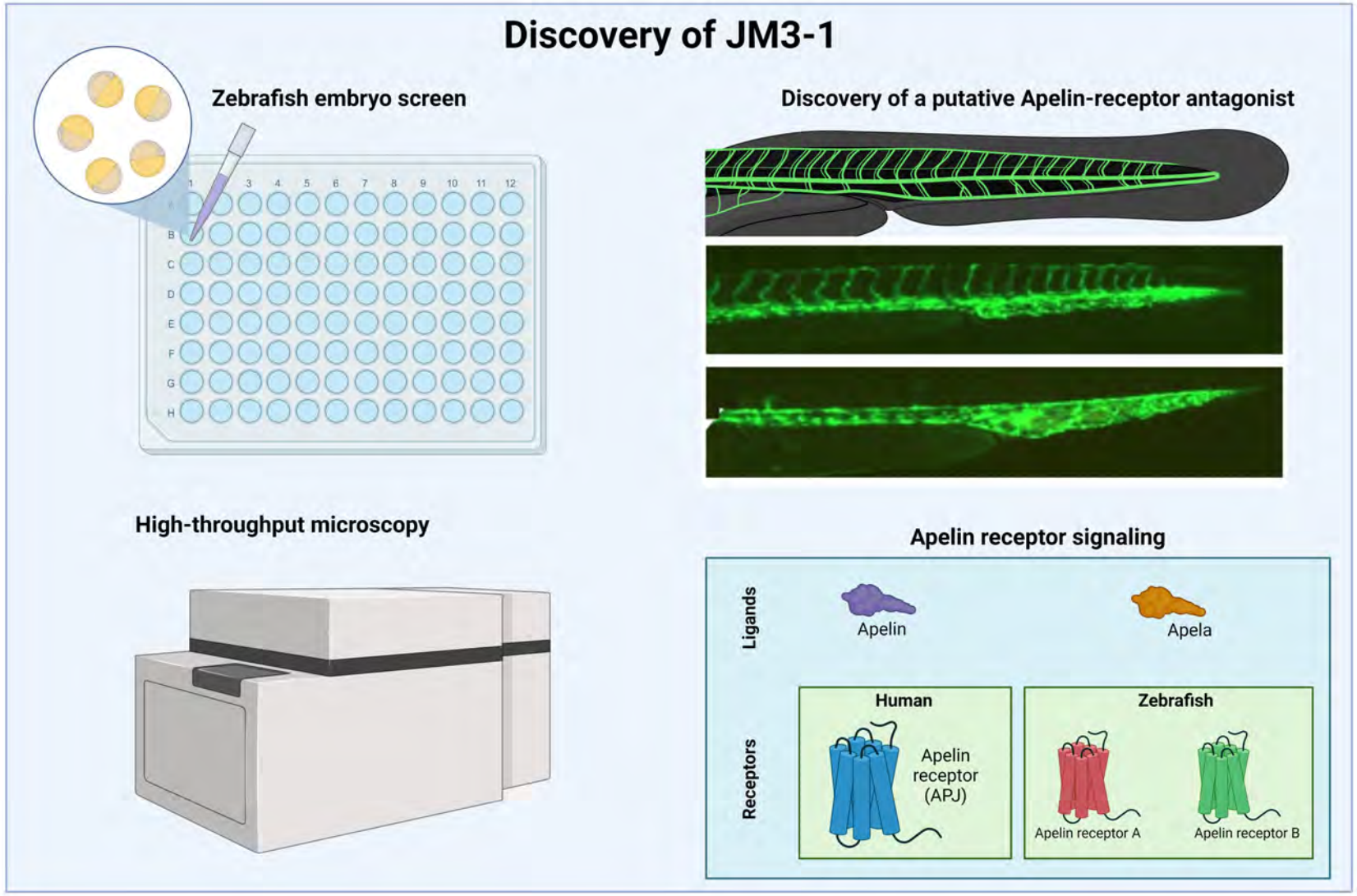
# Novel therapeutics: peptide-based antagonists

Transcription factor dysfunction leads to a range of non-communicable diseases including cancer, diabetes and cardiovascular disease, as well as chronic inflammatory diseases such as rheumatoid arthritis and multiple sclerosis




The TBS Platform allows the efficient screening and identification of peptide-based antagonists that can inhibit disease-relevant targets with high affinity and specificity by inhibiting the protein-protein interactions (PPIs) that targets require for function.

# Using zebrafish to screen for novel bioactive compounds

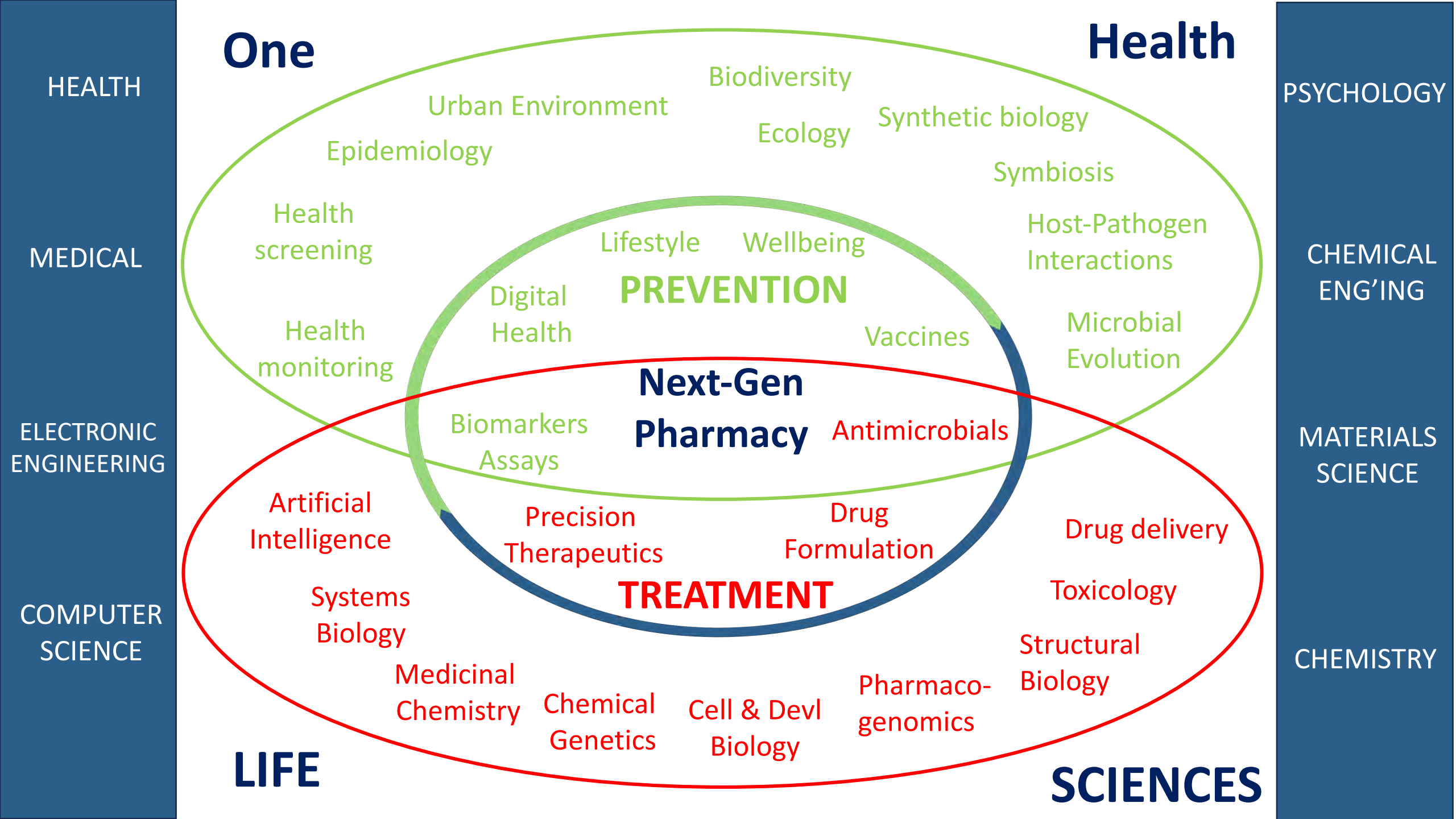



Philip Ingham

UFHealth

UF | Department of Medicinal Chemistry
COLLEGE of PHARMACY

Hendrik Leusch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# The Department of Life Sciences in 2028

## Research

**Centre of excellence for:**

- pathogen surveillance
- biodiversity and conservation
- parasitism and symbiosis in ecosystems and human health
- synthetic biology
- sustainable therapeutics

## Education

**Centre of excellence for:**

- pedagogic innovation
- next-generation pharmacy
- evolution, biodiversity and sustainability

# Thank You for Listening