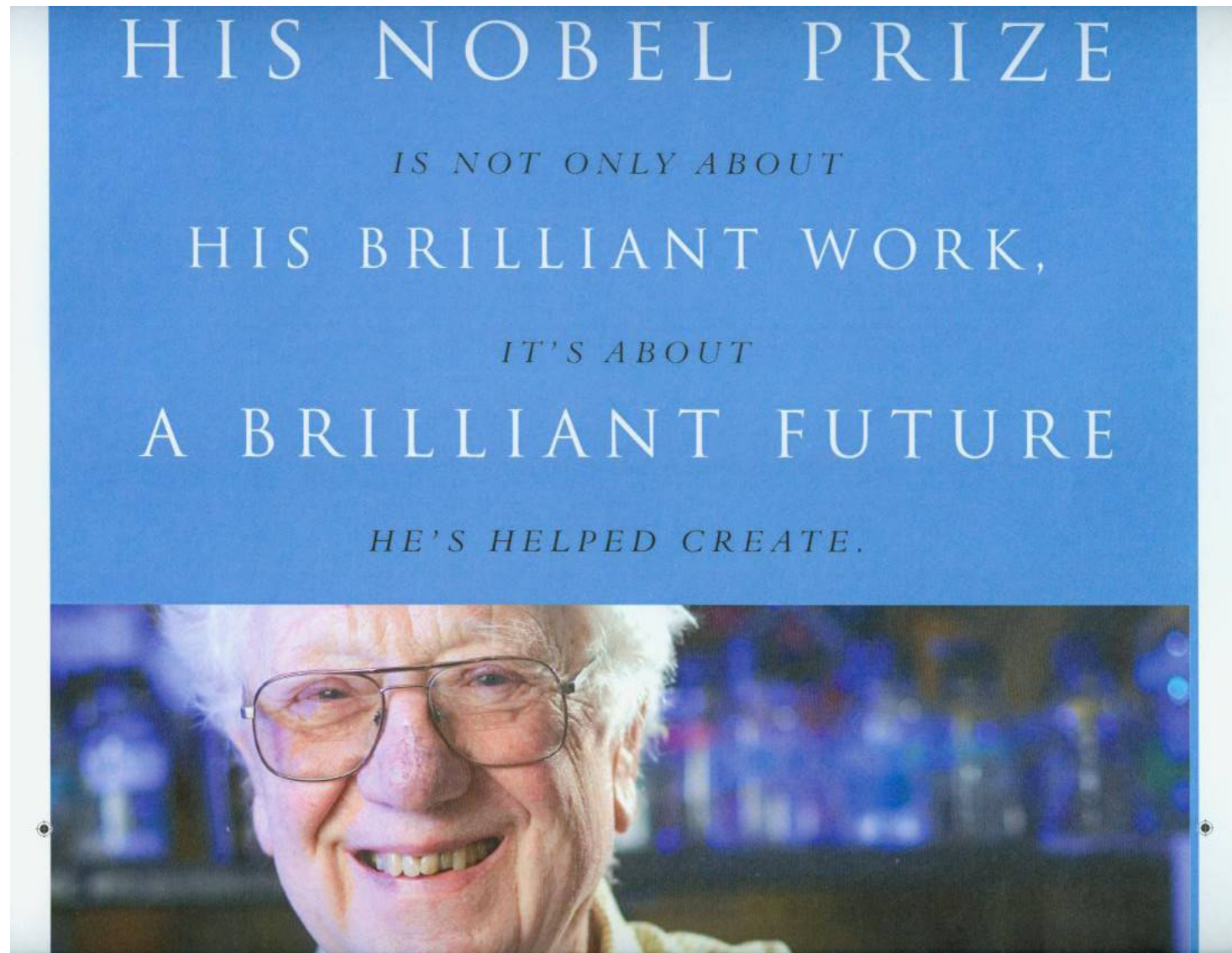
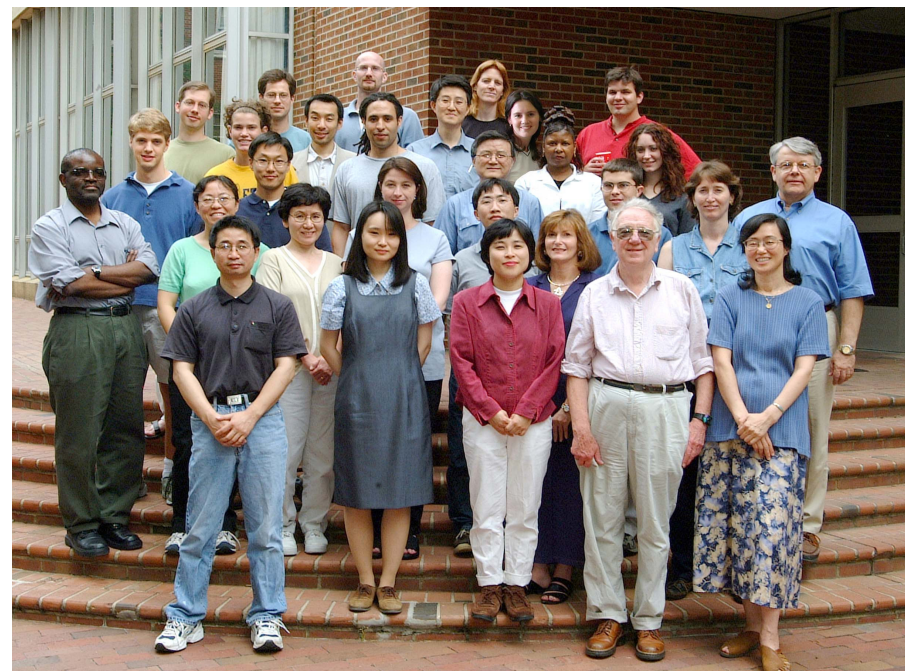


A close view of Oliver Smithies







What I know about Oliver!

- In 2001, Pei-Jane visited me in Chapel Hill and we had the first chance to have dinner with Oliver.
- During the dinner, I found him different from what I thought.



The story from Oliver

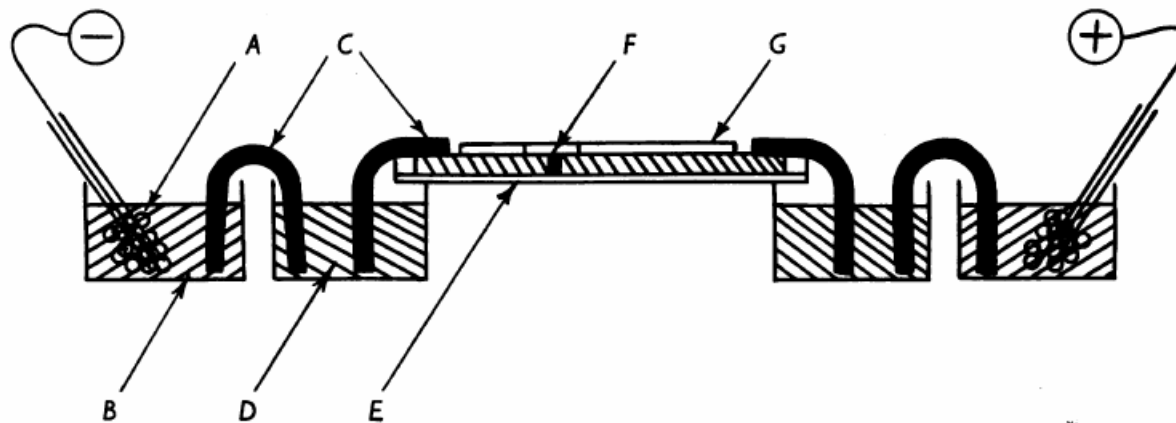
- Oliver Smithies
 - First job in Toronto, Canada (1953)
 - Work on anything but related to insulin
 - Insulin should result from a precursor
 - How to prove it? How to separate them?
 - Electrophoresis before the 1950s
 - First developed in 1937 by Arne Tiselius, recognized by Nobel Prize for Chemistry in 1948
 - Filter paper.



Gel electrophoresis



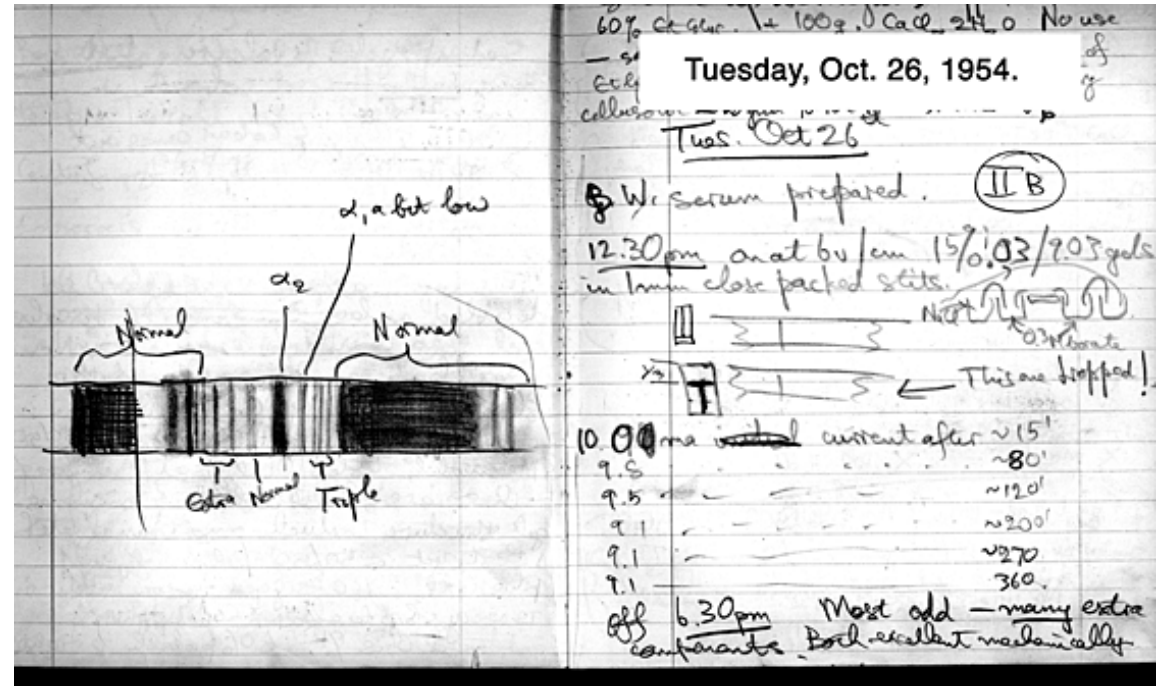
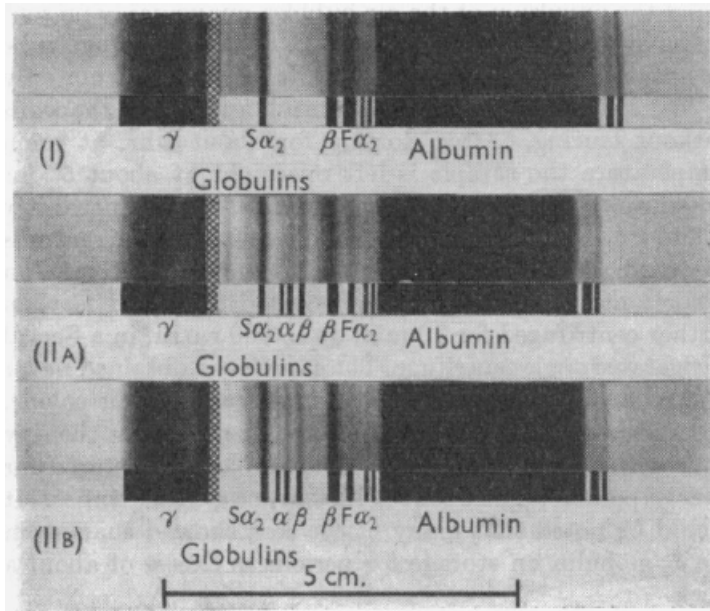
- In 1955, Smithies
 - Used starch, cooked it up, made a jelly, put insulin into the jelly!
 - Gairdner Foundation International Award
 - *For the discovery, development of a technique that had a profound impact on the experimental and clinical analysis of proteins and nucleic acids.*
 - Most quoted paper in biological literature



Smithies, O., Zone electrophoresis in starch gels **group variations in the serum proteins** of normal human adults, *Biochem. J.*, **61**, 629, **1955**

Hereditary factors determine serum groups

- Hepatoglobulin
- *Hp1F, Hp1S, Hp2 (Hp1F-Hp1S)*
 - Homologous unequal crossing over
 - $B-B \times B-B \rightarrow B-B-B \times B$
 - Homologous crossing over is possible!



From Proteins to Protein Genetics

- Cloned 2nd human gene: fetal globin gene
 - $G\gamma$ (Glycine) and $A\gamma$ (Alanine)
 - Human fetal $G\gamma$ and $A\gamma$ -globin genes: complete nucleotide sequences suggest that DNA can be exchanged between these duplicated genes.
Cell 1980 21:627-38.
 - Homologous recombination is possible!
- Cloned β -globin gene
 - Correct abnormal β -globin in patient with sickle cell anemia (Gene therapy)



Thurs. April 22, 1982.

13

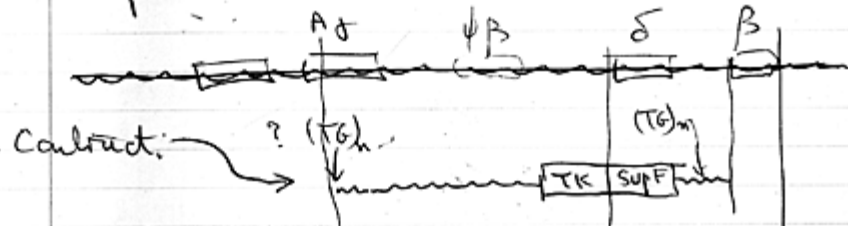
Thurs. April 22nd

Assay for gene placement

Aim: to place corrective DNA in the right place.

Need: as assay for developing techniques.

Proposal:



Transform human TK⁻ cells → grow up
a large # of transformants

Prepare DNA from TK⁺ cells

Cut with rest. enz. → size to

clone in an amber phage

Plate on su^o → screen with β specific probe

Vary (TG)_n or single stranded ends or UV

or BUdR etc. to try to ↑ # positives

Can also treat recipient cells
are found - with agents to ↑ SCE etc.

Selection in eukaryote × selection in prokaryote × β probe selection

Can accept non-linear → Duplication → Elimination → correction



Oliver's notebook

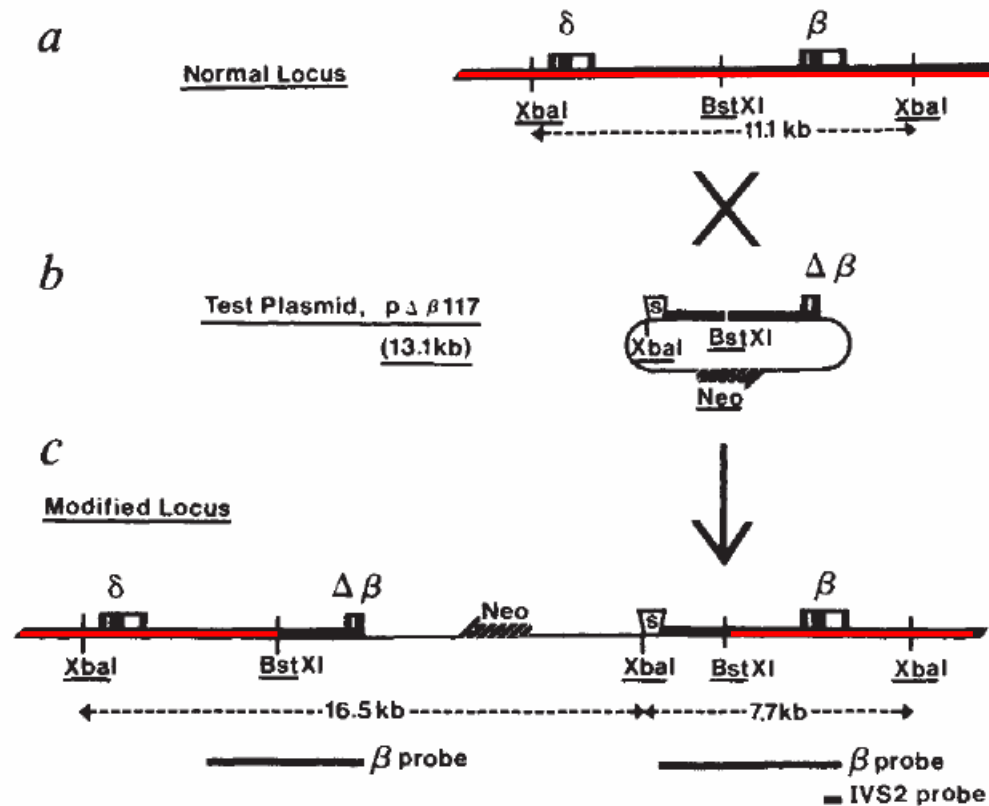
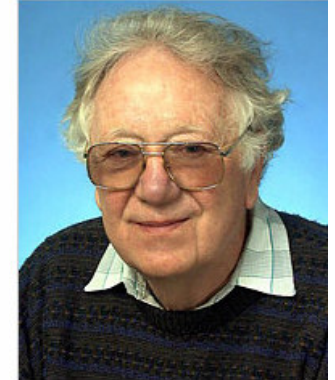
Insertion of DNA sequences into the human chromosomal β -globin locus by homologous recombination

Oliver Smithies*, Ronald G. Gregg*, Sallie S. Boggs†, Michael A. Koralewski* & Raju S. Kucherlapati‡

* Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin 53706, USA

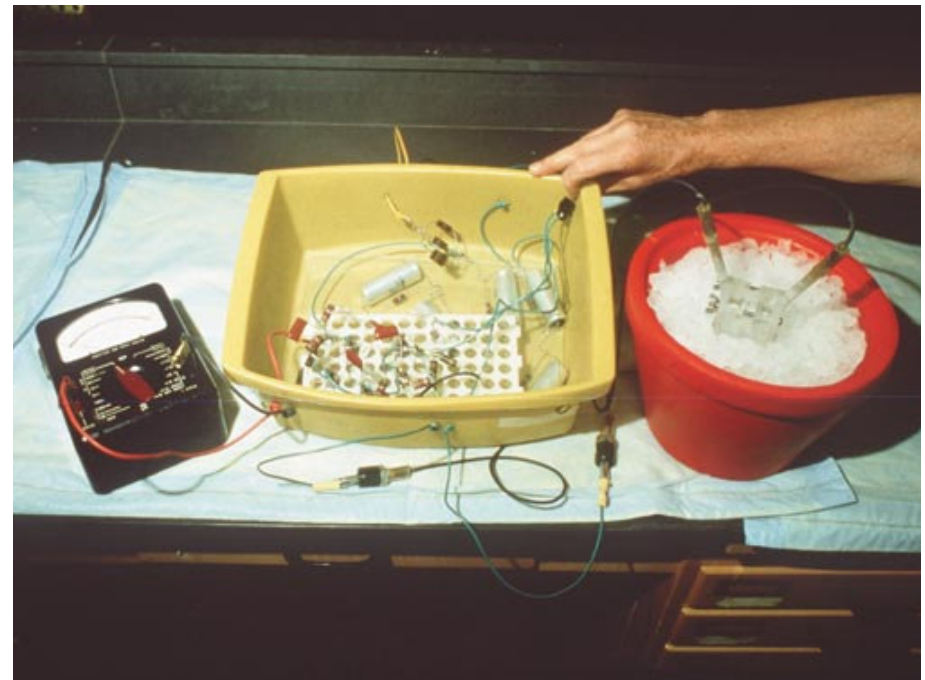
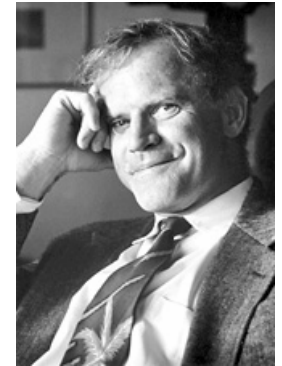
† School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, USA

‡ Center for Genetics, University of Illinois College of Medicine, Chicago, Illinois 60612, USA

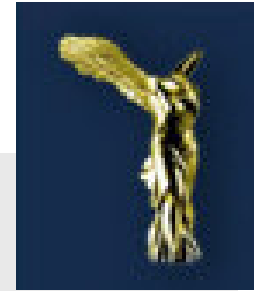


Major hurdles

- PCR: developed by Kary Mullis in 1983
 - Thermocycler: introduced in 1986
- Electroporator: introduce DNA into the cells



2001 Albert Lasker Award



2001 Winners

Albert Lasker Award for Basic Medical Research

Mario Capecchi, Martin Evans, and Oliver Smithies

For the development of a powerful technology for manipulating the mouse genome with exquisite precision, which allows the creation of animal models of human disease.

[Read about the 2001 Award for Basic Medical Research»](#)



Mario Capecchi
University of Utah, Howard Hughes
Medical Institute



Martin Evans
Cardiff University



Oliver Smithies
University of North Carolina at Chapel Hill

He has told me.....



- Who should be awarded with Nobel Prize
 - The work/discovery/invention will not be done without this person.

(before he was awarded the prize)

- *"My work was never toward getting the Nobel Prize" "It was solving a problem, and enjoying the solution."*

(During the interview with Nobel Foundation)

- I think "This is historically important"

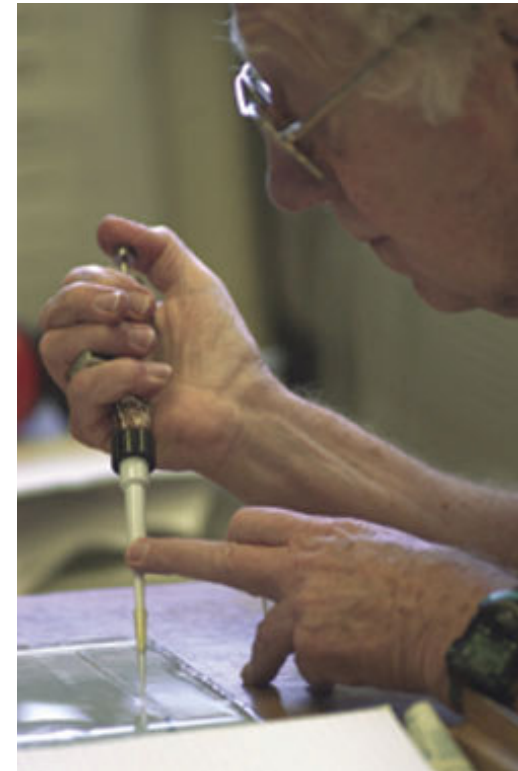
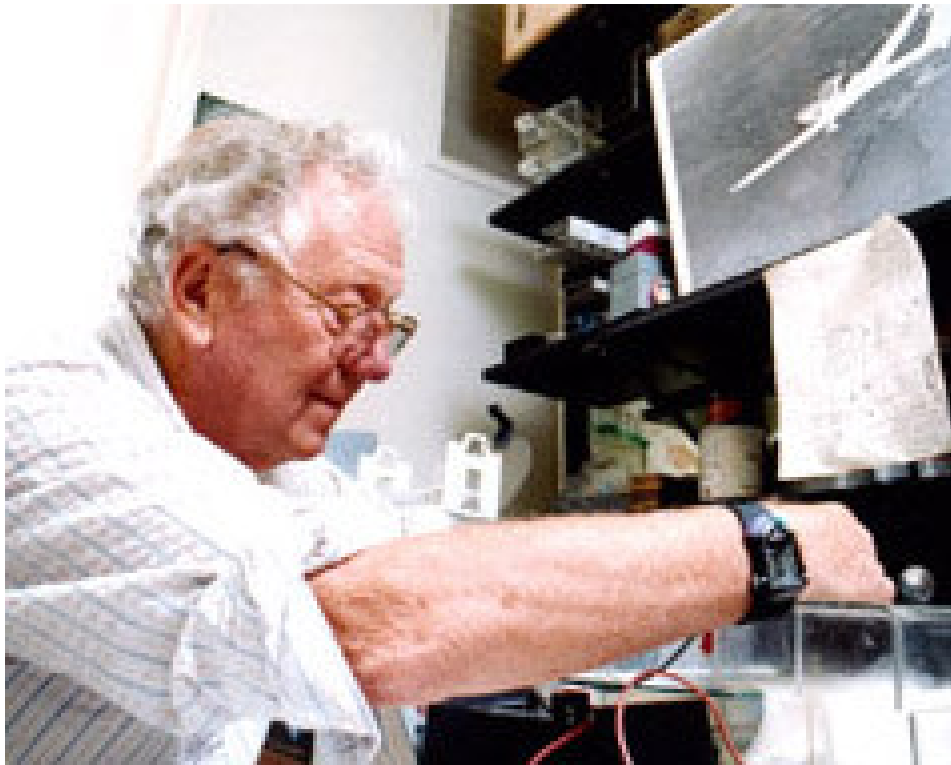
Selected genes knocked out in this Lab

- beta 2-microglobulin
- **CFTR**: *Cystic fibrosis*
- $\beta 1$ and $\beta 2$ adult globin genes: *Thalassemias*
- **ER α** and **ER β**
- ANP, NPRA, NPRC, renin, ATIIR1A, ACE, **eNOS**, NaK2Cl cotransporter, AS, bradykinin B1 and B2 receptor:
Hypertension
- **MIP-1 α** , **COX-1**, **COX-2**, **iNOS**, **CCR2**: *Inflammation*
- Topoisomerase I
- Adrenomedullin
- Timp3, **apoE**, hepatic lipase, apoC-III, apoA-I, apoB:
Atherosclerosis
- Lipoic acid synthase, vitamin C synthase (L-gulonolactone-gamma-oxidase)



His passion for science

- His being at his bench every single day has been my greatest inspiration in research
- *“It’s not the achievements.”* Oliver explains *“It’s got more to do with curiosity, trying to solve problems, understand something.”*

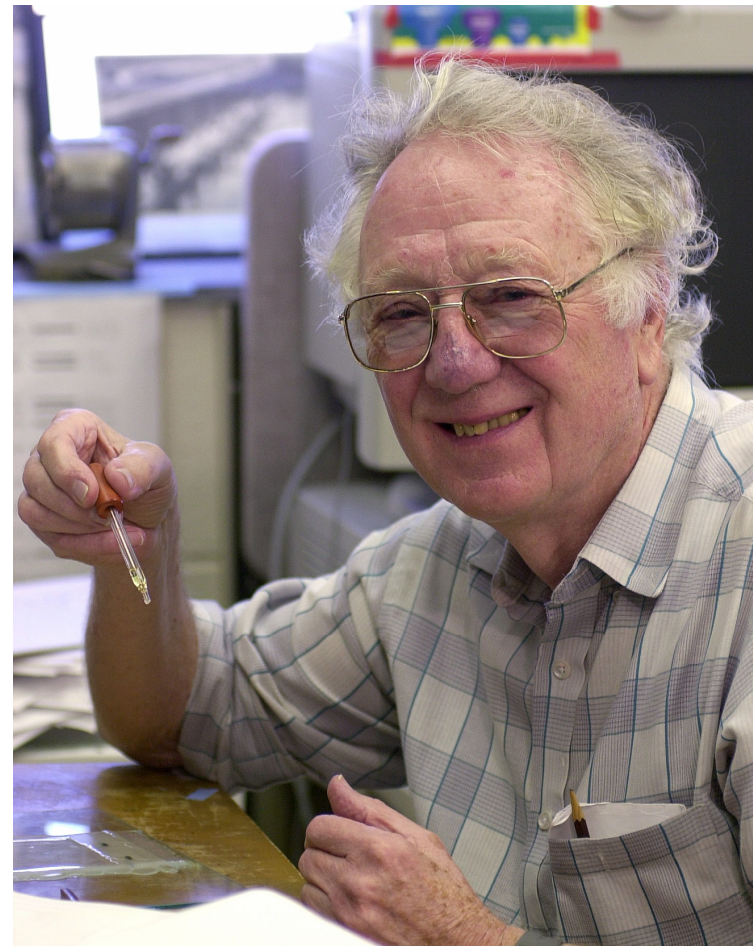




Smithies, UNC "knockout mice" pioneer, receives prestigious Lasker Award – "America's Nobel"

“ If you do work and every day there’s some enjoyment, then the science never gets boring because every day you have something new to look forward to.”

Oliver Smithies



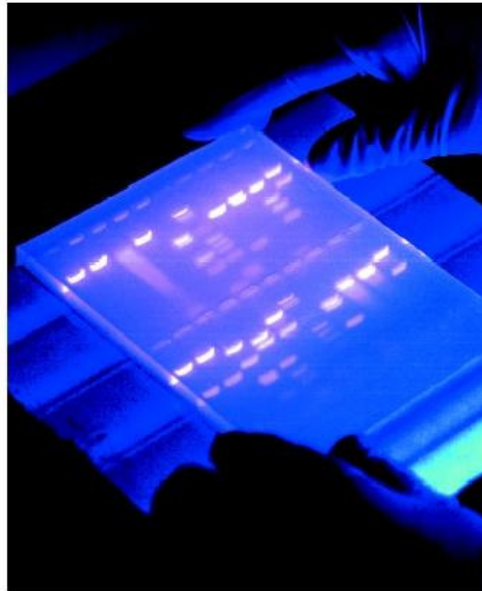
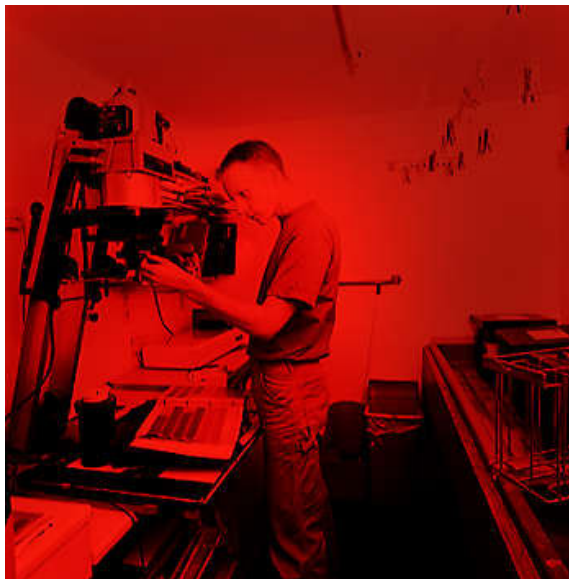
Oliver always enjoys the three things

- He did some science;
- He took Nobuyo to the lunch;
- He went flying.



- **Runway moment:**

- *“It was like coming out of the clouds on a stormy day in your small airplane and finding the runway right in front of you.”*
 - Francis Collins recalled what Oliver said in Gordon Conference
- He called this “runway moment” to describe his moment waiting for seeing the result and getting the real answer.



recapitulate abnormal fat distribution and hypertension phenotypes, but not insulin resistance observed in human patients of comparable mutation (Table 1).

Because the F1 animals we used in our experiments are genetically identical

except for proline or leucine at position 465 of PPAR γ , any phenotypic difference is

directly attributable to this substitution. Thus normal insulin sensitivity in Pparg^{P465L/+}

mice indicates that this mutation ~~per se~~ is not sufficient to cause insulin resistance in

mice. Although genetic background is clearly important for the severity of insulin

resistance in mice^{13,14}, our preliminary glucose tolerance and insulin tolerance tests

indicated that the Pparg^{P465L/+} mice backcrossed to C57BL/6 genetic background were

not insulin resistant compared to their wild type littermates. In addition, although aging

and diet could interact and alter insulin sensitivity, none of the 10-month-old Pparg^{P465L/+}

mice exhibited increased insulin resistance over wild type mice even when they were on

high fat diet for 5 months (unpublished data). While species difference may account for

the normal insulin sensitivity in mice and severe insulin resistance in humans with

comparable mutation, there remains a possibility that the originally identified patients

with P467L mutation may carry additional unidentified genetic modifier(s). Recently,

Savage et al¹⁵ identified human patients with severe insulin resistance who are doubly

heterozygous for frameshift mutations in the genes for PPAR γ and for muscle specific

regulator subunit of protein phosphatase 1. Individuals carrying only one of the

mutations are normal. This digenic inheritance suggests that the level of PPAR γ

expression may be an important modifier but not the cause of insulin resistance, but

can be accompanied by a difference in the expression of a

The patients with the P467L mutation have partial lipodystrophy, with loss of fat

in subcutaneous limb and buttock, but preserved visceral and abdominal subcutaneous

Manuscript corrected by Oliver





John Hagman

It happened!

It happened!!!

What happened?

Are you a
grandfather ?



Jenny Langenbach

Keys to the success

2. Love science

1. Hard work

3. ~~Good wife~~
3. Nice wife



A scientist's scientist



- “He identified critically important problems, he approaches them in the laboratory with his own hands, he comes up with creative ideas, and he makes profoundly important discoveries that change the face of science”
 - by Frances Collins (Director of NHGRI)
- “He is the most gentlemanly, open-minded, non-self-promoting individual you will meet”
 - by Bradley Popovich (President of Sirius Genomics)

- “*Things I learned in this laboratory are not only research, but also the scientific temper and attitude these two distinguished scientists represent. I will always remind myself and apply this standard in my future career.*”
 - By Yau-Sheng Tsai (Dissertation Acknowledgement)

- Careful ***observation*** !
- ***Enjoy*** your work !
- Keep passion for science and be a real scientist !