Cancer genetics - II

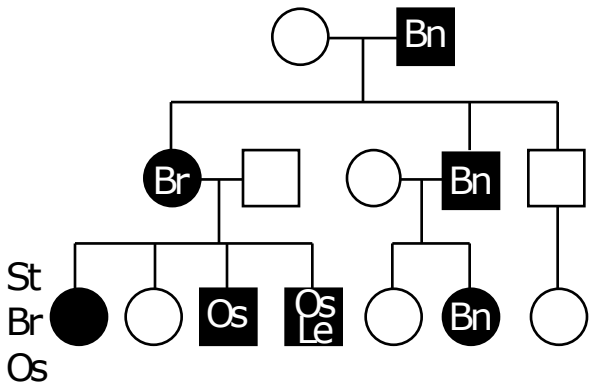
Genetics 371B Lecture 21 5 Nov. 1999

Checkpoint defects and cancer

- **p53 and response to DNA damage:**
  - ◇ p53 synthesis ⬆ (translational control)
  - ◇ cell cycle blocked
  - ◇ sometimes: apoptosis (programmed cell death)

Checkpoint defects may be associated with multiple forms of cancer

e.g., **Li-Fraumeni syndrome** – p53



DNA repair defects and cancer

Discovery of mismatch repair defects in human cancer…

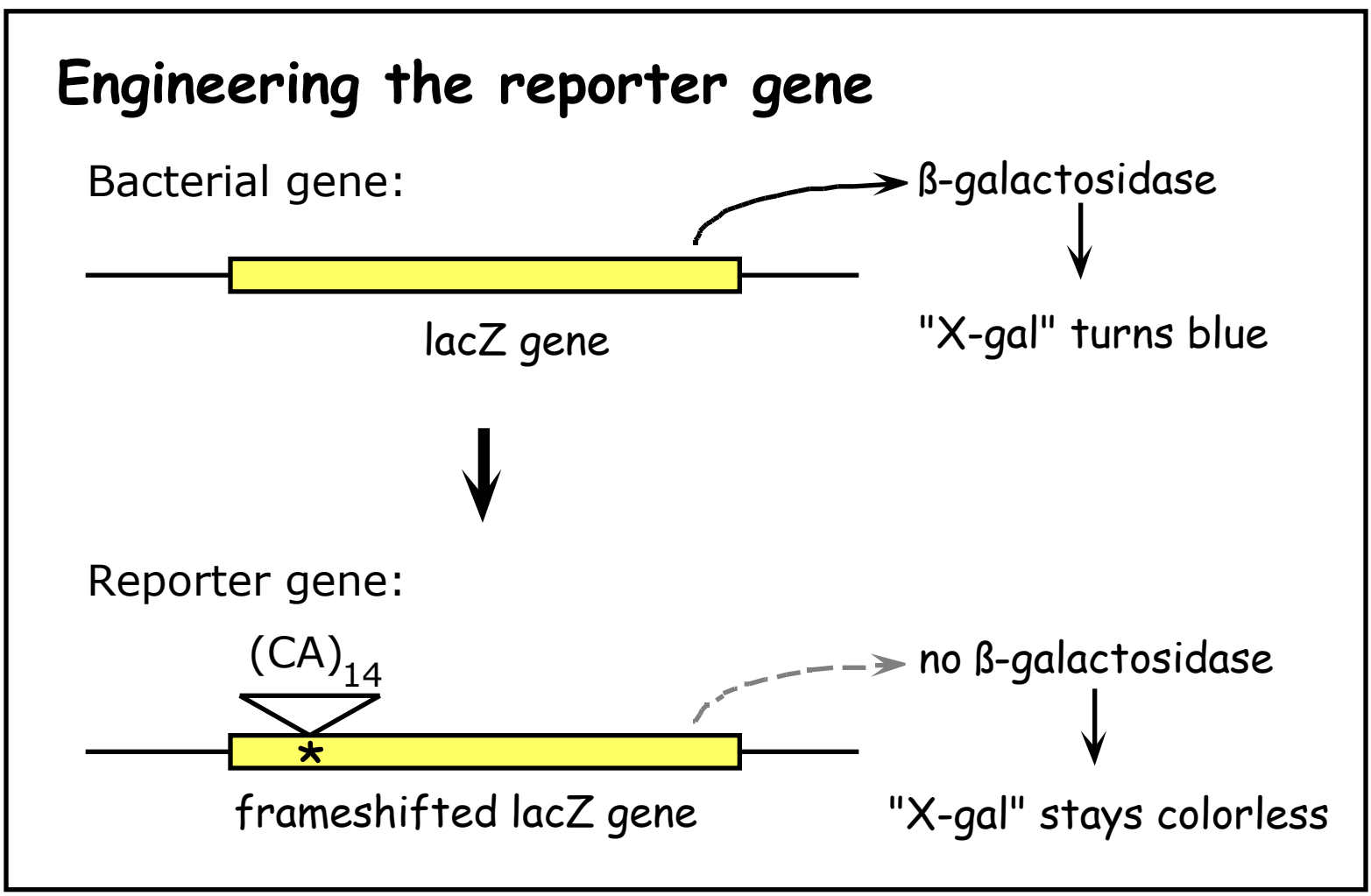
Richard Kolodner, 1992-93

Yeast mismatch repair genes similar to E. coli's?

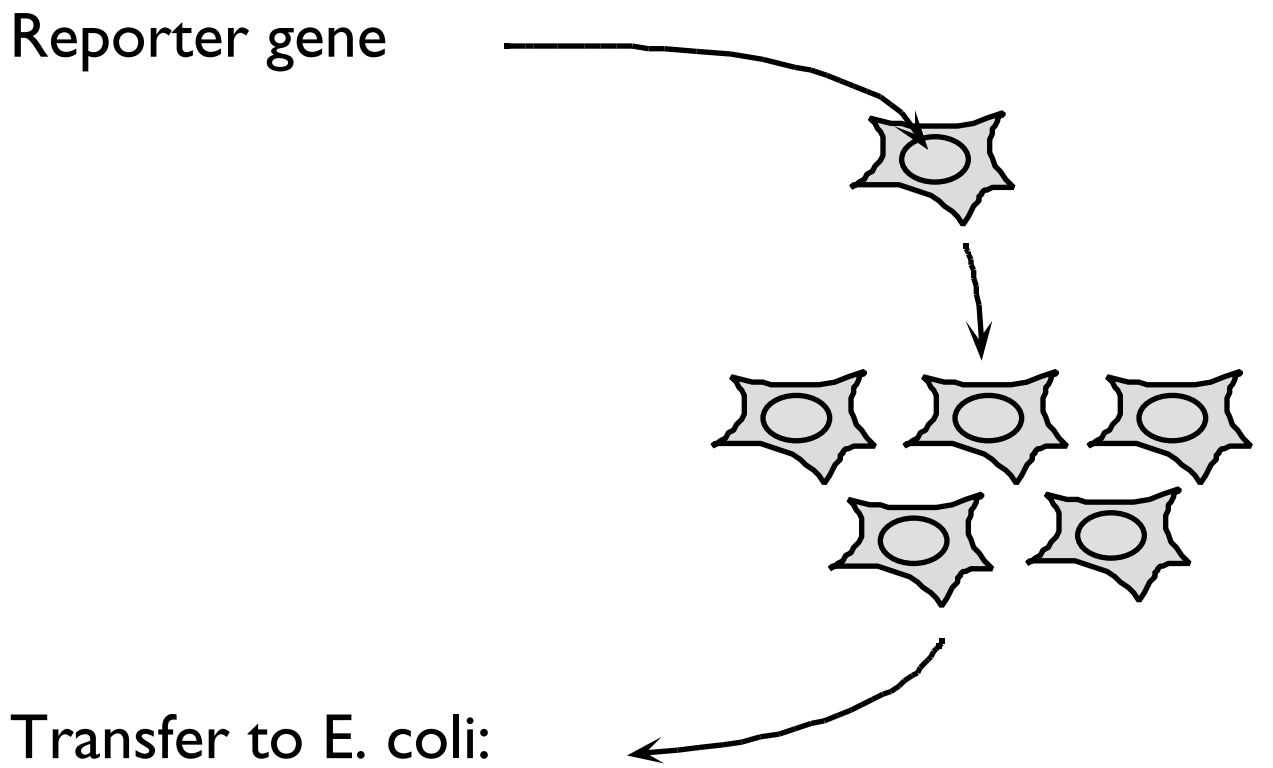
Related gene in humans – Associated with HNPCC (hereditary nonpolyposis colon cancer)

Bert Vogelstein, 1993: Increase in replication errors in HNPCC cells?

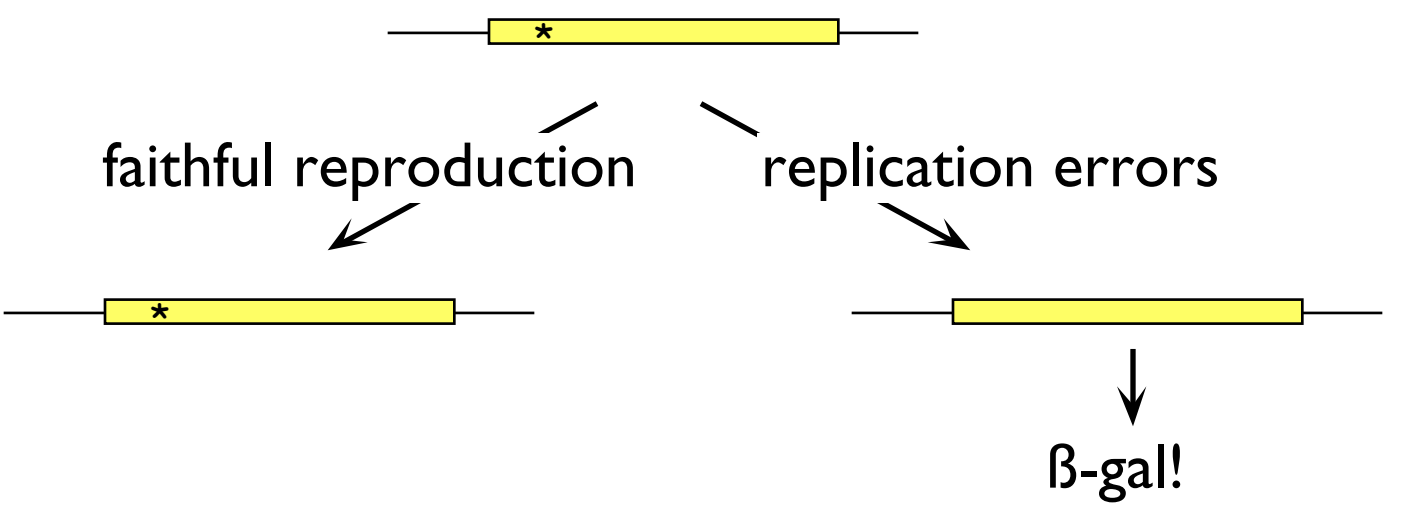
Strategy: Engineer a **reporter gene** that could cause a colorless substrate to become colored… but only if a specific kind of mutation has occurred



The experiment

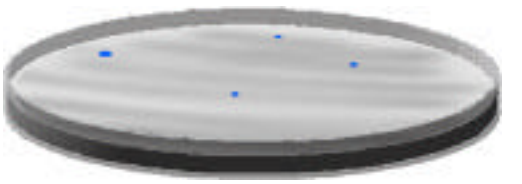


The prediction

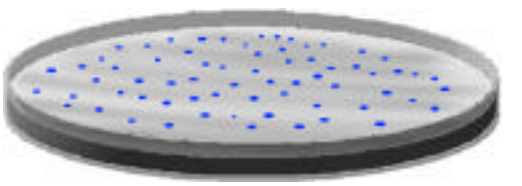


The result

Normal cells ⟶



HNPCC cells ⟶



Replication error rate ~100x up in tumor cells!

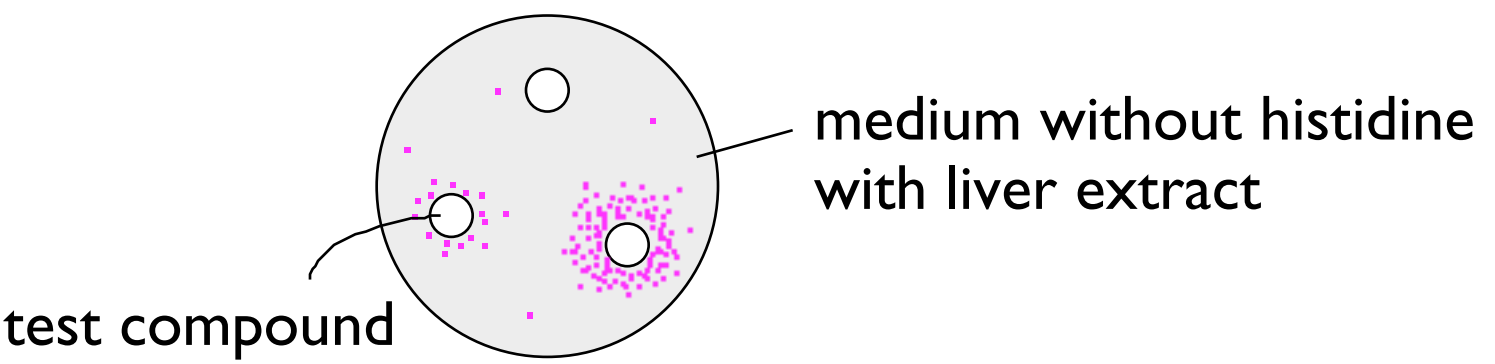
Testing for mutagens (...potential carcinogens)

The Ames test …Bruce Ames

Premise: Start with **his**$^-$ Salmonella mutants (no growth w/o histidine)

base substitution
frameshift

treat with test compound:
his$^+$ revertants?



Cancer drug screening: The
"**Seattle Project**"

Lee Hartwell & Stephen Friend

Premise: Use yeast mutants to screen chemotherapeutic agents for specific defects

Practice questions

1. A tumor the size of a marble, about 1 cubic centimeter in volume, may contain 10^9 cells. How many cell *generations* (starting from a single cell) are required to produce this tumor? How many cell *divisions* were involved?

2. Some uterine tumors consist of as many as 10^{11} cells. In women heterozygous for a particular X-linked gene, researchers have discovered that *every* cell of such a tumor has the *same* active X-linked allele. Explain this observation in terms of the Lyon hypothesis.

3. Although it is generally agreed that the path to malignancy is a multistep process, Weinberg and his colleagues were able to transform tissue culture cells in *one* step. Suggest an explanation for this apparent discrepancy.

4. The proto-oncogene erbB encodes the cell surface receptor for a growth factor. Binding of growth factor to the receptor signals the cell to divide. Speculate on how a mutation in the erbB proto-oncogene might lead to malignancy.

5. Researchers have found that breast cancer is not common among *homozygotes* affected with ataxia-telangiectasia, but breast cancer is the most frequent type of cancer among *heterozygotes* for A-T. The researchers think that this oddity might be a consequence of the ages of the people in the two groups. Can you give a reasonable explanation?