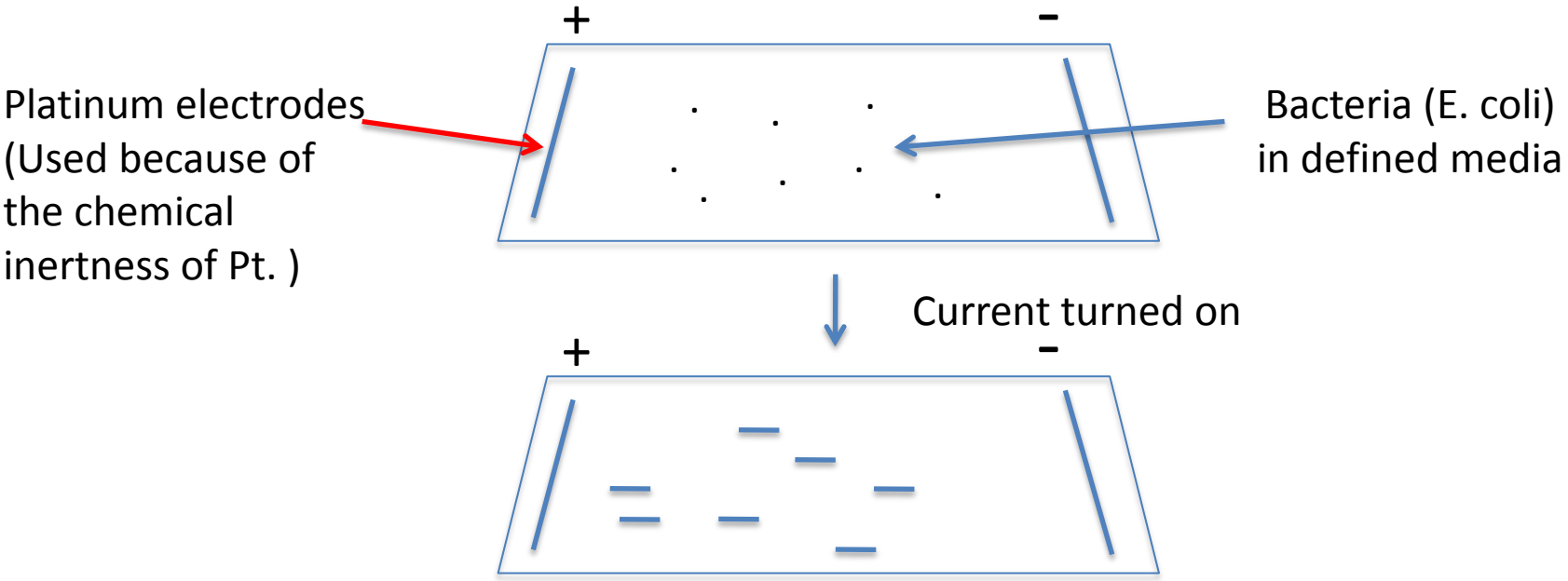
Discovery of cisplatin

Dr. Barnett Rosenberg at Michigan St. University designed an experiment to examine the effect of electric current on bacterial growth. Rosenberg et al. 1965. Nature 205: 698-699.



About 1-2 hours after the current is turned on the E.coli are about 300 times longer than normal. They have grown in length but not divided!
Does this demonstrate that an electric current prevents E. coli division?

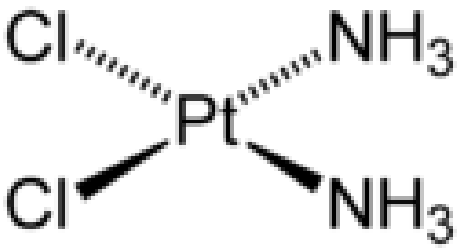
What controls could be performed?

Controls

- Incubate bacteria without current turned on.
- Measure current in apparatus.
- When the current was turned off the bacteria gradually returned (1-2 hour) to their normal size.
- Media without bacteria was treated in an electric field and then bacteria were incubated in the “electrocuted” media without an electric current. Why?
- Individual components of the defined media were made, subject to electrolysis and then tested for oxidizing agents. Why?

Cisplatin

- Reaction of $(NH_4)_2SO4$ with the platinum electrode (in the presence of oxygen) created cisplatin.
- Rosenberg suspected this possibility based on previous literature and directly tested $PtCl_4(NH_4)_2$ the bacteria showed the same effect as in the electric field.
- Rosenberg tested several different compounds on human cancer cell lines and the most effective was cisplatin $PtCl_2(NH_3)_2$



http://www.youtube.com/watch?v=QfXc9gIt_hM

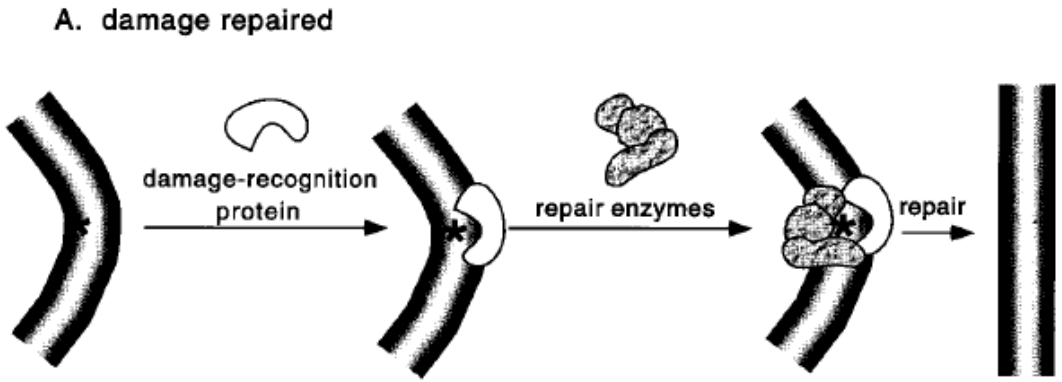
Cisplatin: discovery of a cancer drug

- It covalently binds to DNA and if the resulting damage cannot be repaired, then the cells enter apoptosis (die). Cisplatin damages DNA in all cells but cancer cells divide more often so they generally sustain more damage.
- Cisplatin is used to treat metastatic testicular cancer, metastatic ovarian cancer, advanced bladder cancer and others.
- Cisplatin has side effects that include nausea, diarrhea, low white blood cell count, change in how food tastes, and decreased bone marrow effectiveness.
- How are these side effects connected?

Why do some cells die more efficiently than others after cisplatin treatment?

- If cells repair the damage from cisplatin they survive. If they do not, then they die (enter apoptosis).
- Some proteins (e.g. high mobility group proteins, HMG) bind cisplatin lesions with high affinity and prevent DNA repair.
- “One hypothesis, which has been proposed in various studies, suggests that the binding of these proteins *(HMGB1)* to platinum-DNA adducts blocks the removal of DNA lesions, thereby enhancing the sensitivity of cells to cisplatin.” from: Wei, et al. J. Biol. Chem. 278: 1769-1773.

Cisplatin Repair versus No Repair



Hypothesis: Inhibition of DNA repair by HMG protein binding leads to apoptosis.

Figure 2. Schematic representation of the modes of action of the two classes of proteins that specifically recognize *cis*-platin-damaged DNA sites. *A*) Binding of damage–recognition proteins to DDP-modified sites attracts the enzymatic components of the repair machinery, leading to repair of the lesion. *B*) Binding of abundant architectural proteins such as HMG1 and H1 to damaged sites interferes with repair by preventing the damage recognition proteins from interacting with such sites.

From: Zaltanova J. (1998) FASEB J. 12: 791-799.

Give an example of how you could test this theory?