Part III: If it’s *Really* Broke, Break it Some More!
DNA Damage and Cancer Therapy

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DNA Damage → Cancer

DNA Damage → Cancer therapy

Better forms of cancer treatment
Bari, Italy: Dec. 2, 1943

German *Luftwaffe* conducted an air raid on ships in harbor at the Italian seaport of Bari.
Bari, Italy: Dec. 2, 1943

SS John Harvey was among the ships destroyed.
Bari, Italy: Dec. 2, 1943

SS John Harvey’s top secret cargo:
2000 mustard gas bombs (60 tonnes)
Aftermath of Bari air raid

- 628 military victims; 83 deaths
- Unknown number of civilian injuries/deaths
- Doctors noticed low white blood cell counts; people were dying because their bone marrow cells stopped dividing
A high dose of mustard gas causes bone marrow cells to stop dividing.

Could a lower dose cause cancer cells to stop dividing?
1946: First cancer “chemotherapy” study declassified

December, 1942: First treatment of a cancer patient by mustard gas compound **mustine** by doctors at Yale University, working for U.S. Army

"The problem was fundamental and simple: could one destroy a tumor with [nitrogen mustard] before destroying the host."  – Alfred Gilman, 1963

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[trials.yale.edu](https://trials.yale.edu)
“Within forty-eight hours after the initiation of therapy a softening of the tumor masses was detected. It soon became obvious that this was not wishful thinking. [...] by the tenth day, when the series of injections was terminated, [neck tumors] were no longer palpable and a few days later the [under-arm tumors] had completely receded.”

– A. Gilman, 1963
How did a chemical warfare agent cause tumor regression?

1) Why is it toxic to cells?
2) Why is it more toxic to cancer cells than to normal cells?
How did a chemical warfare agent cause tumor regression?

1) Why is it toxic to cells?

It causes DNA damage
How did a chemical warfare agent cause tumor regression?

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Inter-strand crosslink
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Inter-strand crosslink
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Inter-strand crosslink

Questions?!
How did a chemical warfare agent cause tumor regression?

ICL repair: 1) DNA “surgery”
How did a chemical warfare agent cause tumor regression?

ICL repair: 2) Synthesis of DNA across the crosslink
How did a chemical warfare agent cause tumor regression?

ICL repair: 2) Synthesis of DNA across the lesion
How did a chemical warfare agent cause tumor regression?

ICL repair: 2) Synthesis of DNA across the lesion
How did a chemical warfare agent cause tumor regression?

ICL repair: 3) Removal of chemical junk
How did a chemical warfare agent cause tumor regression?

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ICL repair: 3) Removal of chemical junk
How did a chemical warfare agent cause tumor regression?

1) More DNA surgery
2) Use unbroken DNA as a template to repair broken DNA.

ICL repair: 4) Double-strand break repair
How did a chemical warfare agent cause tumor regression?

ICL repair: 4) Double-strand break repair
ICLs can be lethal when not repaired fast enough

Division failure; catastrophic chromosome damage

Cellular auto-destruct mechanism (apoptosis)

Movie courtesy John Bachman, Sorger lab
2) Why are DNA crosslinking agents more toxic to cancer cells than to normal cells?
Effect of ICLs on dividing vs. non-dividing cells

Non-dividing cell

Only slightly toxic at low doses
Random unlikely to land in crucial gene.

Interstrand-crosslinking agent

Dividing cell

More toxic:
1) Inhibits replication,
2) Fixing it involves dangerous DNA “surgery”
Most toxic of all.
Uncontrolled division → less time to repair the damage.
Another reason cancer cells are more sensitive to DNA damage: DNA repair machines are often broken in cancer cells!
Other forms of DNA crosslinking chemotherapy

- Nitrogen mustards
  - Mustine, cyclophosphamide, chlorambucil, ifofosamide
- Platinum compounds
  - Cisplatin, oxaliplatin, carboplatin
- Mitomycin C
Other forms of DNA-damaging cancer therapy

Other chemicals that cause DNA damage:

- Camptothecin
- Etoposide
- Doxorubicin
- Bleomycin
- Nucleotide anti-metabolites

Radiation therapy

www.mayo.edu
Side-effects of chemo are mostly because of it poisons normal cells that divide quickly.

- Hair loss
- Nausea
- Bone marrow

wikipedia.org

bcl.med.harvard.edu
Epilogue: Results in the first chemotherapy patient, 1942

“[...] the bone marrow slowly recovered
[...] the tumor regenerated with the bone marrow.
A subsequent shorter course of therapy resulted in only transient improvement and a third course had very little effect.”

- A. Gilman, 1963
Problems with chemotherapy

Evolution of resistance

Side-effects

- Hair loss
- Anemia
- Nausea

Evolution of resistance
Which DNA damage repair machines are broken? → Make the corresponding kind of DNA damage

Normal cell

Cancer cell
Making the right kind of damage: PARP inhibitors

Goal: Target cancer cells with messed-up double-strand break repair.

1) DNA surgery
2) Use unbroken DNA as a template to repair broken DNA.
Making the right kind of damage: PARP inhibitors

Goal: Target cells with messed-up double-strand break repair.

Uh oh…Here comes DNA replication!
Making the right kind of damage: PARP inhibitors
Making the right kind of damage: PARP inhibitors
Making the right kind of damage: PARP inhibitors
“[...The] Congress is totally committed to provide the funds that are necessary, whatever is necessary, for the conquest of cancer. The President is totally committed [...]

– Richard Nixon, upon signing the National Cancer Act of 1971

“[The stimulus package] will launch a new effort to conquer a disease that has touched the life of nearly every American, including me, by seeking a cure for cancer in our time.”

– Barack Obama, 2009
“a cure for cancer”
“a cure for cancer”

“a cure for disease”
“a cure for each different cancer”

“an effective treatment for each different cancer”
My at-home diagnosis system says I may have cancer.

Ah yes. It appears you do. Don't worry, we can treat that.

...and your insurance will gladly pay for it.

Biopsy; DNA extraction; sequencing

Determine which genes are mutated:
1) What is driving growth? 2) What DNA repair machines are messed up?

Precise chemotherapy
"Targeted therapy"

Viral therapy?
Immunotherapy?
Gene therapy?

Cancer therapy in the future

Oct. 10 SITN Lecture:
Biotechnology and the Emergence of New Therapeutics

Nov. 28 SITN Lecture:
What's in Your Genes: whole genome sequencing and its impact on personalized medicine
Thank you!

*SITN would like to acknowledge the following organizations for their generous support.*

**Harvard Medical School**
Office of Communications and External Relations
Division of Medical Sciences

The Harvard Graduate School of Arts and Sciences (GSAS)

The Harvard Graduate Student Council (GSC)

The Harvard Biomedical Graduate Students Organization (BGSO)

The Harvard/MIT COOP