Hopkins treated all invasive cervical carcinomas with radium, a white radioactive metal that glows an eerie blue.

When radium was first discovered in the late 1800s, headlines nationwide hailed it as “a substitute for gas, electricity, and a positive cure for every disease.” Watchmakers added it to paint to make watch dials glow, and doctors administered it in powdered form to treat everything from seasickness to ear infections. But radium destroys any cells it encounters, and patients who’d taken it for trivial problems began dying. Radium causes mutations that can turn into cancer, and at high doses it can burn the skin off a person’s body. But it also kills cancer cells.

Hopkins had been using radium to treat cervical cancer since the early 1900s, when a surgeon named Howard Kelly visited Marie and Pierre Curie, the couple in France who’d discovered radium and its ability to destroy cancer cells. Without realizing the danger of contact with radium, Kelly brought some back to the United States in his pockets and regularly traveled the world collecting more. By the 1940s, several studies—one of them conducted by Howard Jones, Henrietta’s physician—showed that radium was safer and more effective than surgery for treating invasive cervical cancer.
Cervical cancer is caused by the human papillomavirus (HPV)
HPV vaccines are now available
Gleevec: Treatment for CML
Blood smears: what’s different?

Normal blood

Chronic myeloid leukemia (CML)
Diagnosis of CML

• Rare disease: 5000 new cases/year in US
• Can occur at any age, but most common after age 50
• CML doesn’t always have obvious symptoms: feeling run-down, weight loss, abdominal pain
• Diagnosed by high white blood cell count, usually in chronic phase
Phases of CML

Chronic Phase
• Blast cells <5%
• Lasts months to years

Accelerated Phase
• Blast cells ~15%
• Lasts weeks to months

Blast Crisis
• Blast cells >30%
• Can metastasize
• “Aggressive acute leukemia”

“Blast” cells
Over 95% of CML cases have a translocation between chromosomes 9 and 22
BCR-ABL: fusion tyrosine kinase

- Reciprocal translocation results in a fusion protein
- ABL has tyrosine kinase activity
- BCR-ABL is more highly expressed than wild-type ABL → oncogene
Why BCR-ABL leads to cancer
Gleevec: The “Magic Bullet” Against Cancer

• In the late 1990s, Gleevec was identified by Novartis in a high-throughput screen for tyrosine kinase inhibitors.
• Dr. Brian Druker at Oregon Health and Science University demonstrated that Gleevec inhibits proliferation of BCR-Abl-expressing hematopoietic cells
• Gleevec received FDA approval in May 2001
Gleevec: HOW IT WORKS

Diagram showing the mechanism of action of Gleevec:
- Left side: CML Enzyme binds ATP, leading to the formation of Cancer Protein, which results in CML.
- Right side: Gleevec blocks the binding of ATP to the CML Enzyme, preventing the formation of Cancer Protein and thus preventing CML.
Gleevec: a tyrosine kinase inhibitor

- Small molecule inhibitor
- Displaces ATP and prevents binding
- Traps the BCR-ABL kinase domain in an inactive form
- Remarkably specific, little interaction with other kinases
Gleevec treatment: cheap and simple

• Taken orally once/twice daily
• Easy to vary dosage as needed
• Side effects: nausea, headache, muscle soreness, swelling
• Cost $20 – 30 per pill, generic imatinib cheaper
Gleevec Treatment: effective

Recent studies have shown a 95.2% survival rate over 8 years for CML patients treated with Gleevec – similar to that of the general population.
TARGETED TREATMENT

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential
Can we “starve” a tumor?

**HOW TO STARVE A TUMOR**

1. As a cancer tumor grows, it builds its own network of capillaries that tap into the body’s blood supply and draw on the oxygen and nutrients the tumor needs to survive.

   - Capillaries
   - Tumor

2. Drugs that block angiogenesis—the formation of new vessels—cut the tumor off from its blood supply. Gradually, malignant cells die and the tumor starts to shrink.

   - Anti-angiogenesis drugs
   - Destroyed capillary
   - Dying cancer cells

TIME Graphic by Joe Lertola
Without Angiogenesis, Tumor Growth Stops

With Angiogenesis, Tumor Growth Proceeds

http://www.youtube.com/watch?v=k90CXzUVrvl&feature=related
Angiogenesis and Regulatory Proteins

Concentration of Angiogenesis Inhibitors

- Inhibitors high
- Activators low

- Inhibitors low
- Activators high

Rare cell division

Frequent cell division

Blood vessel
### Activators of Angiogenesis

#### Some Naturally Occurring Activators of Angiogenesis

**Proteins**
- Acidic fibroblast growth factor
- Angiogenin
- Basic fibroblast growth factor (bFGF)
- Epidermal growth factor
- Granulocyte colony-stimulating factor
- Hepatocyte growth factor
- Interleukin 8
- Placental growth factor
- Platelet-derived endothelial growth factor
- Scatter factor
- Transforming growth factor alpha
- Tumor necrosis factor alpha
- **Vascular endothelial growth factor (VEGF)**

**Small Molecules**
- Adenosine
- 1-Butyryl glycerol
- Nicotinamide
- Prostaglandins E1 and E2

Artwork by Jeanna Kelly © 2002
Anti-angiogenesis Cancer Treatments!

As researchers have turned their focus to creating therapies that can interfere with angiogenesis by targeting the VEGF protein.

By inhibiting the VEGF protein, the blood supply to a tumor may be gradually reduced.
Avastin:
The First Anti-Angiogenesis Treatment For Cancer

VEGF | VEGFR-2
---|---
Endothelial cell | Intracellular

**ANGIOGENESIS**
Angiogenesis is mediated primarily through the interaction between VEGF and VEGFR-2

**ANGIOGENESIS**
Avastin inhibits VEGF extracellularly and therefore, may inhibit angiogenesis without disrupting targets outside the VEGF pathway
Avastin: The First Anti-Angiogenesis Treatment For Cancer

In 1993, Genentech produced a monoclonal antibody that specifically binds to VEGF.

In 2004, FDA approved the antibody, known as Avastin® (bevacizumab), became the first commercially available anti-angiogenesis treatment for cancer.

In 2011, FDA approval for treatment of breast cancer was revoked due to lack of benefits as well as risk from side effects.
TARGET OTHER PARTS OF THE VEGF SIGNALLING PATHWAY

Sunitinib maleate
Butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(-diethylamino)ethyl]-5-[(Z)5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1); C_{22}H_{27}FN_{2}O_{2} • C_{4}H_{6}O_{5}; M_{r} = 532.6; CAS number: 557795-19-4

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Nature Reviews | Drug Discovery
Agents Targeting the VEGF Pathway

- **Anti-VEGF antibodies**
  (eg, bevacizumab)

- **Soluble VEGF receptors**
  (eg, VEGF-Trap)

- **Anti-VEGFR antibodies**
  (eg, IMC-1121b)

- **Small-molecule VEGFR inhibitors**
  (eg, vatalanib, sunitinib, ZD6474, AZD2171)

Endothelial cell

- VEGFR-1
- VEGFR-2

- Survival
- Proliferation
- Migration

**ANGIOGENESIS**
Like drug resistance, some cancer cells respond to therapy by shifting their dependence to a different hallmark capability.

This has occurred in response to some anti-angiogenic therapies.

In response to some potent angiogenesis inhibitors, tumors shift from depending on continuing angiogenesis to increasing invasiveness and metastasis (Azam et al., 2010; Ebos et al., 2009; Bergers and Hanahan, 2008).

By invading nearby tissues, initially hypoxic cancer cells evidently gain access to normal, preexisting tissue vasculature.