NIH NATIONAL CANCER INSTITUTE

Targeted Cancer Therapies

What are targeted cancer therapies?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted drugs," "molecularly targeted therapies," "precision medicines," or similar names.

Targeted therapies differ from standard chemotherapy in several ways:

- Targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells.
- Targeted therapies are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells.
- Targeted therapies are often cytostatic (that is, they block tumor cell proliferation), whereas standard chemotherapy agents are cytotoxic (that is, they kill tumor cells).

Targeted therapies are currently the focus of much anticancer drug development. They are a cornerstone of precision medicine, a form of medicine that uses information about a person's genes and proteins to prevent, diagnose, and treat disease.

Many targeted cancer therapies have been approved by the Food and Drug Administration (FDA) to treat specific types of cancer. Others are being studied in clinical trials (research studies with people), and many more are in preclinical testing (research studies with animals).

How are targets for targeted cancer therapies identified?

The development of targeted therapies requires the identification of good targets—that is, targets that play a key role in cancer cell growth and survival. (It is for this reason that targeted therapies are sometimes referred to as the product of "rational" drug design.)

One approach to identify potential targets is to compare the amounts of individual proteins in cancer cells with those in normal cells. Proteins that are present in cancer cells but not normal cells or that are more abundant in cancer cells would be potential targets, especially if they are known to be involved in cell growth or survival. An example of such a differentially expressed target is the human epidermal growth factor receptor 2 protein (HER-2). HER-2 is expressed at high levels on the surface of some cancer cells. Several targeted therapies are directed against HER-2, including trastuzumab (Herceptin), which is approved to treat certain breast and stomach cancers that overexpress HER-2.

Another approach to identify potential targets is to determine whether cancer cells produce mutant (altered) proteins that drive cancer progression. For example, the cell growth signaling protein BRAF is present in an altered form (known as BRAF V600E) in many melanomas. Vemurafenib (Zelboraf) targets this mutant form of the BRAF protein and is approved to treat patients with inoperable or metastatic melanoma that contains this altered BRAF protein.

Researchers also look for abnormalities in chromosomes that are present in cancer cells but not in normal cells. Sometimes these chromosome abnormalities result in the creation of a fusion gene (a gene that incorporates parts of two different genes) whose product, called a fusion protein, may drive cancer development. Such fusion proteins are potential targets for targeted cancer therapies. For example, imatinib mesylate (Gleevec) targets the BCR-ABL fusion protein, which is made from pieces of two genes that get joined together in some leukemia cells and promotes the growth of leukemic cells.

How are targeted therapies developed?

Once a candidate target has been identified, the next step is to develop a therapy that affects the target in a way that interferes with its ability to promote cancer cell growth or survival. For example, a targeted therapy could reduce the activity of the target or prevent it from binding to a receptor that it normally activates, among other possible mechanisms.

Most targeted therapies are either small molecules or monoclonal antibodies. Small-molecule compounds are typically developed for targets that are located inside the cell because such agents are able to enter cells relatively easily. Monoclonal antibodies are relatively large and generally cannot enter cells, so they are used only for targets that are outside cells or on the cell surface.

Candidate small molecules are usually identified in what are known as "high-throughput screens," in which the effects of thousands of test compounds on a specific target protein are examined. Compounds that affect the target (sometimes called "lead compounds") are then chemically modified to produce numerous closely related versions of the lead compound. These related compounds are then tested to determine which are most effective and have the fewest effects on nontarget molecules.

Monoclonal antibodies are developed by injecting animals (usually mice) with purified target proteins, causing the animals to make many different types of antibodies against the target. These antibodies are then tested to find the ones that bind best to the target without binding to nontarget proteins.

Before monoclonal antibodies are used in humans, they are "humanized" by replacing as much of the mouse antibody molecule as possible with corresponding portions of human antibodies. Humanizing is necessary to prevent the human immune system from recognizing the monoclonal antibody as "foreign" and destroying it before it has a chance to bind to its target protein. Humanization is not an issue for small-molecule compounds because they are not typically recognized by the body as foreign.

What types of targeted therapies are available?

Many different targeted therapies have been approved for use in cancer treatment. These therapies include hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers,

angiogenesis inhibitors, immunotherapies, and toxin delivery molecules.

- **Hormone therapies** slow or stop the growth of hormone-sensitive tumors, which require certain hormones to grow. Hormone therapies act by preventing the body from producing the hormones or by interfering with the action of the hormones. Hormone therapies have been approved for both breast cancer and prostate cancer.
- **Signal transduction inhibitors** block the activities of molecules that participate in signal transduction, the process by which a cell responds to signals from its environment. During this process, once a cell has received a specific signal, the signal is relayed within the cell through a series of biochemical reactions that ultimately produce the appropriate response(s). In some cancers, the malignant cells are stimulated to divide continuously without being prompted to do so by external growth factors. Signal transduction inhibitors interfere with this inappropriate signaling.
- **Gene expression modulators** modify the function of proteins that play a role in controlling gene expression.
- **Apoptosis inducers** cause cancer cells to undergo a process of controlled cell death called apoptosis. Apoptosis is one method the body uses to get rid of unneeded or abnormal cells, but cancer cells have strategies to avoid apoptosis. Apoptosis inducers can get around these strategies to cause the death of cancer cells.
- **Angiogenesis inhibitors** block the growth of new blood vessels to tumors (a process called tumor angiogenesis). A blood supply is necessary for tumors to grow beyond a certain size because blood provides the oxygen and nutrients that tumors need for continued growth. Treatments that interfere with angiogenesis may block tumor growth. Some targeted therapies that inhibit angiogenesis interfere with the action of vascular endothelial growth factor (VEGF), a substance that stimulates new blood vessel formation. Other angiogenesis inhibitors target other molecules that stimulate new blood vessel growth.
- **Immunotherapies** trigger the immune system to destroy cancer cells. Some immunotherapies are monoclonal antibodies that recognize specific molecules on the surface of cancer cells. Binding of the monoclonal antibody to the target molecule results in the immune destruction of cells that express that target molecule. Other monoclonal antibodies bind to certain immune cells to help these cells better kill cancer cells.
- **Monoclonal antibodies that deliver toxic molecules** can cause the death of cancer cells specifically. Once the antibody has bound to its target cell, the toxic molecule that is linked to the antibody—such as a radioactive substance or a poisonous chemical—is taken up by the cell, ultimately killing that cell. The toxin will not affect cells that lack the target for the antibody—i.e., the vast majority of cells in the body.

Cancer vaccines and **gene therapy** are sometimes considered targeted therapies because they interfere with the growth of specific cancer cells. Information about cancer vaccines can be found in NCI's Cancer Treatment Vaccines page.

How is it determined whether a patient is a candidate for targeted therapy?

For some types of cancer, most patients with that cancer will have an appropriate target for a particular targeted therapy and, thus, will be candidates to be treated with that therapy. CML is an example: most patients have the

BCR-ABL fusion gene. For other cancer types, however, a patient's tumor tissue must be tested to determine whether or not an appropriate target is present. The use of a targeted therapy may be restricted to patients whose tumor has a specific gene mutation that codes for the target; patients who do not have the mutation would not be candidates because the therapy would have nothing to target.

Sometimes, a patient is a candidate for a targeted therapy only if he or she meets specific criteria (for example, their cancer did not respond to other therapies, has spread, or is inoperable). These criteria are set by the FDA when it approves a specific targeted therapy.

What are the limitations of targeted cancer therapies?

Targeted therapies do have some limitations. One is that cancer cells can become resistant to them. Resistance can occur in two ways: the target itself changes through mutation so that the targeted therapy no longer interacts well with it, and/or the tumor finds a new pathway to achieve tumor growth that does not depend on the target.

For this reason, targeted therapies may work best in combination. For example, a recent study found that using two therapies that target different parts of the cell signaling pathway that is altered in melanoma by the BRAF V600E mutation slowed the development of resistance and disease progression to a greater extent than using just one targeted therapy (1).

Another approach is to use a targeted therapy in combination with one or more traditional chemotherapy drugs. For example, the targeted therapy trastuzumab (Herceptin) has been used in combination with docetaxel, a traditional chemotherapy drug, to treat women with metastatic breast cancer that overexpresses the protein HER2/neu.

Another limitation of targeted therapy at present is that drugs for some identified targets are difficult to develop because of the target's structure and/or the way its function is regulated in the cell. One example is Ras, a signaling protein that is mutated in as many as one-quarter of all cancers (and in the majority of certain cancer types, such as pancreatic cancer). To date, it has not been possible to develop inhibitors of Ras signaling with existing drug development technologies. However, promising new approaches are offering hope that this limitation can soon be overcome.

What are the side effects of targeted cancer therapies?

Scientists had expected that targeted cancer therapies would be less toxic than traditional chemotherapy drugs because cancer cells are more dependent on the targets than are normal cells. However, targeted cancer therapies can have substantial side effects.

The most common side effects seen with targeted therapies are diarrhea and liver problems, such as hepatitis and elevated liver enzymes. Other side effects seen with targeted therapies include:

- Skin problems (acneiform rash, dry skin, nail changes, hair depigmentation)
- Problems with blood clotting and wound healing
- High blood pressure

- Gastrointestinal perforation (a rare side effect of some targeted therapies)

Certain side effects of some targeted therapies have been linked to better patient outcomes. For example, patients who develop acneiform rash (skin eruptions that resemble acne) while being treated with the signal transduction inhibitors erlotinib (Tarceva) or gefitinib (Iressa), both of which target the epidermal growth factor receptor, have tended to respond better to these drugs than patients who do not develop the rash (2). Similarly, patients who develop high blood pressure while being treated with the angiogenesis inhibitor bevacizumab generally have had better outcomes (3).

The few targeted therapies that are approved for use in children can have different side effects in children than in adults, including immunosuppression and impaired sperm production (4).

What targeted therapies have been approved for specific types of cancer?

The FDA has approved targeted therapies for the treatment of some patients with the following types of cancer (some targeted therapies have been approved to treat more than one type of cancer):

Bladder cancer: Atezolizumab (Tecentriq), nivolumab (Opdivo), avelumab (Bavencio), pembrolizumab (Keytruda), erdafitinib (Balversa), enfortumab vedotin-ejfv (Padcev)

Brain cancer: Bevacizumab (Avastin), everolimus (Afinitor)

Breast cancer: Everolimus (Afinitor), tamoxifen (Nolvadex), toremifene (Fareston), trastuzumab (Herceptin), fulvestrant (Faslodex), anastrozole (Arimidex), exemestane (Aromasin), lapatinib (Tykerb), letrozole (Femara), pertuzumab (Perjeta), ado-trastuzumab emtansine (Kadcyla), palbociclib (Ibrance), ribociclib (Kisqali), neratinib maleate (Nerlynx), abemaciclib (Verzenio), olaparib (Lynparza), talazoparib tosylate (Talzenna), atezolizumab (Tecentriq), alpelisib (Piqray), fam-trastuzumab deruxtecan-nxki (Enhertu), tucatinib (Tukysa), sacituzumab govitecan-hziy (Trodelvy), pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo), pembrolizumab (Keytruda), margetuximab-cmkb (Margenza)

Cervical cancer: Bevacizumab (Avastin), pembrolizumab (Keytruda)

Colorectal cancer: Cetuximab (Erbitux), panitumumab (Vectibix), bevacizumab (Avastin), ziv-aflibercept (Zaltrap), regorafenib (Stivarga), ramucirumab (Cyramza), nivolumab (Opdivo), ipilimumab (Yervoy), encorafenib (Braftovi), pembrolizumab (Keytruda)

Dermatofibrosarcoma protuberans: Imatinib mesylate (Gleevec)

Endocrine/neuroendocrine tumors: Lanreotide acetate (Somatuline Depot), avelumab (Bavencio), lutetium Lu 177-dotatate (Lutathera), iobenguane I 131 (Azedra)

Endometrial cancer: Pembrolizumab (Keytruda), lenvatinib mesylate (Lenvima)

Esophageal cancer: Trastuzumab (Herceptin), ramucirumab (Cyramza), pembrolizumab (Keytruda), nivolumab (Opdivo), fam-trastuzumab deruxtecan-nxki (Enhertu)

Head and neck cancer: Cetuximab (Erbitux), pembrolizumab (Keytruda), nivolumab (Opdivo)

Gastrointestinal stromal tumor: Imatinib mesylate (Gleevec), sunitinib (Sutent), regorafenib (Stivarga), avapritinib (Ayvakit), ripretinib (Qinlock)

Giant cell tumor: Denosumab (Xgeva), pexidartinib hydrochloride (Turalio)

Kidney cancer: Bevacizumab (Avastin), sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), temsirolimus (Torisel), everolimus (Afinitor), axitinib (Inlyta), nivolumab (Opdivo), cabozantinib (Cabometyx), lenvatinib mesylate (Lenvima), ipilimumab (Yervoy), pembrolizumab (Keytruda), avelumab (Bavencio)

Leukemia: Tretinoin (Vesanoid), imatinib mesylate (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), rituximab (Rituxan), alemtuzumab (Campath), ofatumumab (Arzerra), obinutuzumab (Gazyva), ibrutinib (Imbruvica), idelalisib (Zydelig), blinatumomab (Blincyto), venetoclax (Venclexta), ponatinib hydrochloride (Iclusig), midostaurin (Rydapt), enasidenib mesylate (Idhifa), inotuzumab ozogamicin (Besponsa), tisagenlecleucel (Kymriah), gemtuzumab ozogamicin (Mylotarg), rituximab and hyaluronidase human (Rituxan Hycela), ivosidenib (Tibsovo), duvelisib (Copiktra), moxetumomab pasudotox-tdfk (Lumoxiti), glasdegib maleate (Daurismo), gilteritinib (Xospata), tagraxofusp-erzs (Elzonris), acalabrutinib (Calquence)

Liver and bile duct cancer: Sorafenib (Nexavar), regorafenib (Stivarga), nivolumab (Opdivo), lenvatinib mesylate (Lenvima), pembrolizumab (Keytruda), cabozantinib (Cabometyx), ramucirumab (Cyramza), ipilimumab (Yervoy), pemigatinib (Pemazyre), atezolizumab (Tecentriq), bevacizumab (Avastin)

Lung cancer: Bevacizumab (Avastin), crizotinib (Xalkori), erlotinib (Tarceva), gefitinib (Iressa), afatinib dimaleate (Gilotrif), ceritinib (LDK378/Zykadia), ramucirumab (Cyramza), nivolumab (Opdivo), pembrolizumab (Keytruda), osimertinib (Tagrisso), necitumumab (Portrazza), alectinib (Alecensa), atezolizumab (Tecentriq), brigatinib (Alunbrig), trametinib (Mekinist), dabrafenib (Tafinlar), durvalumab (Imfinzi), dacomitinib (Vizimpro), lorlatinib (Lorbrena), entrectinib (Rozlytrek), capmatinib hydrochloride (Tabrecta), ipilimumab (Yervoy), selpercatinib (Retevmo), pralsetinib (Gavreto), cemiplimab-rwlc (Libtayo), tepotinib hydrochloride (Tepmetko)

Lymphoma: Ibritumomab tiuxetan (Zevalin), denileukin diftitox (Ontak), brentuximab vedotin (Adcetris), rituximab (Rituxan), vorinostat (Zolinza), romidepsin (Istodax), bexarotene (Targretin), bortezomib (Velcade), pralatrexate (Folotyn), ibrutinib (Imbruvica), siltuximab (Sylvant), idelalisib (Zydelig), belinostat (Beleodaq), obinutuzumab (Gazyva), nivolumab (Opdivo), pembrolizumab (Keytruda), rituximab and hyaluronidase human (Rituxan Hycela), copanlisib hydrochloride (Aliqopa), axicabtagene ciloleucel (Yescarta), acalabrutinib (Calquence), tisagenlecleucel (Kymriah), venetoclax (Venclexta), mogamulizumab-kpkc (Poteligeo), duvelisib (Copiktra), polatuzumab vedotin-piiq (Polivy), zanubrutinib (Brukinsa), tazemetostat hydrobromide (Tazverik), selinexor (Xpovio), tafasitamab-cxix (Monjuvi), brexucabtagene autoleucel (Tecartus), crizotinib (Xalkori), umbralisib tosylate (Ukoniq), lisocabtagene maraleucel (Breyanzi)

Malignant mesothelioma: Ipilimumab (Yervoy), nivolumab (Opdivo)

Microsatellite instability-high or mismatch repair-deficient solid tumors: Pembrolizumab (Keytruda)

Multiple myeloma: Bortezomib (Velcade), carfilzomib (Kyprolis), panobinostat (Farydak), daratumumab (Darzalex), ixazomib citrate (Ninlaro), elotuzumab (Empliciti), selinexor (Xpovio), isatuximab-irfc (Sarclisa), daratumumab and hyaluronidase-fihj (Darzalex Faspro), belantamab mafodotin-blmf (Blenrep)

Myelodysplastic/myeloproliferative disorders: Imatinib mesylate (Gleevec), ruxolitinib phosphate (Jakafi), fedratinib hydrochloride (Inrebic)

Neuroblastoma: Dinutuximab (Unituxin), naxitamab-gqgk (Danyelza)

Ovarian epithelial/fallopian tube/primary peritoneal cancers: Bevacizumab (Avastin), olaparib (Lynparza), rucaparib camsylate (Rubraca), niraparib tosylate monohydrate (Zejula)

Pancreatic cancer: Erlotinib (Tarceva), everolimus (Afinitor), sunitinib (Sutent), olaparib (Lynparza)

Plexiform neurofibroma: Selumetinib sulfate (Koselugo)

Prostate cancer: Cabazitaxel (Jevtana), enzalutamide (Xtandi), abiraterone acetate (Zytiga), radium 223 dichloride (Xofigo), apalutamide (Erleada), darolutamide (Nubeqa), rucaparib camsylate (Rubraca), olaparib (Lynparza)

Skin cancer: Vismodegib (Erivedge), sonidegib (Odomzo), ipilimumab (Yervoy), vemurafenib (Zelboraf), trametinib (Mekinist), dabrafenib (Tafinlar), pembrolizumab (Keytruda), nivolumab (Opdivo), cobimetinib (Cotellic), alitretinoin (Panretin), avelumab (Bavencio), encorafenib (Braftovi), binimetinib (Mektovi), cemiplimab-rwlc (Libtayo), atezolizumab (Tecentriq)

Soft tissue sarcoma: Pazopanib (Votrient), alitretinoin (Panretin), tazemetostat hydrobromide (Tazverik)

Solid tumors that are tumor mutational burden-high (TMB-H): Pembrolizumab (Keytruda)

Solid tumors with an *NTRK* gene fusion: Larotrectinib sulfate (Vitrakvi), entrectinib (Rozlytrek)

Stomach (gastric) cancer: Pembrolizumab (Keytruda), trastuzumab (Herceptin), ramucirumab (Cyramza), fam-trastuzumab deruxtecan-nxki (Enhertu)

Systemic mastocytosis: Imatinib mesylate (Gleevec), midostaurin (Rydapt)

Thyroid cancer: Cabozantinib (Cometriq), vandetanib (Caprelsa), sorafenib (Nexavar), lenvatinib mesylate (Lenvima), trametinib (Mekinist), dabrafenib (Tafinlar), selpercatinib (Retevmo), pralsetinib (Gavreto)

Where can I find information about clinical trials of targeted therapies?

Both FDA-approved and experimental targeted therapies for specific types of cancer are being studied in clinical trials. Descriptions of ongoing clinical trials that are testing types of targeted therapies in cancer patients can be accessed by searching NCI's list of cancer clinical trials. NCI's list of cancer clinical trials includes all NCI-supported clinical trials that are taking place across the United States and Canada, including the NIH Clinical Center in Bethesda, MD. For information about other ways to search the list, see Help Finding NCI-Supported Clinical Trials.

Alternatively, call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) for information about clinical trials of targeted therapies.

Selected References

1. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *New England Journal of Medicine* 2012; 367(18):1694-1703. [PubMed Abstract]
2. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: A literature-based meta-analysis of 24 trials. *Lung Cancer* 2012; 78(1):8-15. [PubMed Abstract]
3. Cai J, Ma H, Huang F, et al. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. *World Journal of Surgical Oncology* 2013; 11:306. [PubMed Abstract]
4. Gore L, DeGregori J, Porter CC. Targeting developmental pathways in children with cancer: what price success? *Lancet Oncology* 2013; 4(2):e70-78. [PubMed Abstract]

Related Resources

Angiogenesis Inhibitors

Hormone Therapy for Breast Cancer

Hormone Therapy for Prostate Cancer

Immunotherapy to Treat Cancer

The RAS Initiative

Updated: March 12, 2021

Cancer Signaling and Targeted Therapy

SEP 03-16-2022

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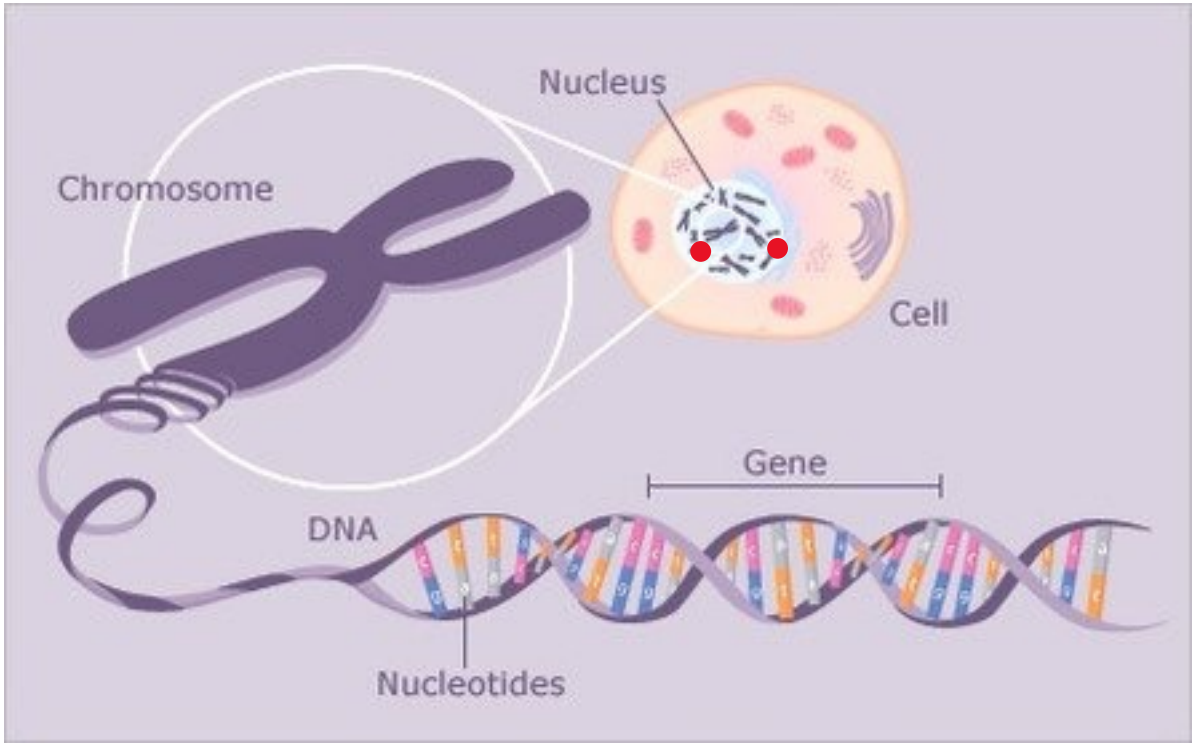
What is a gene?



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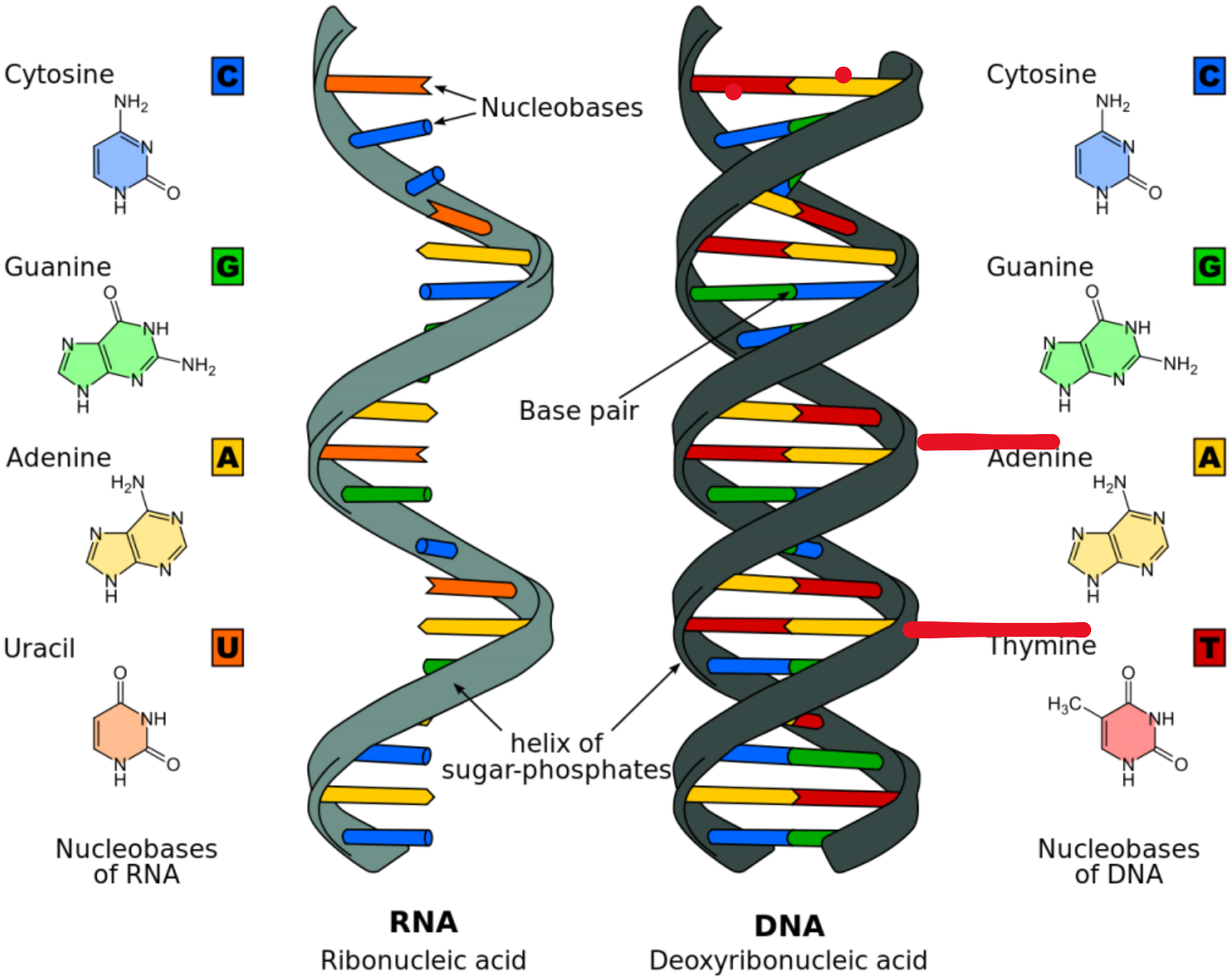
What is a gene made of?



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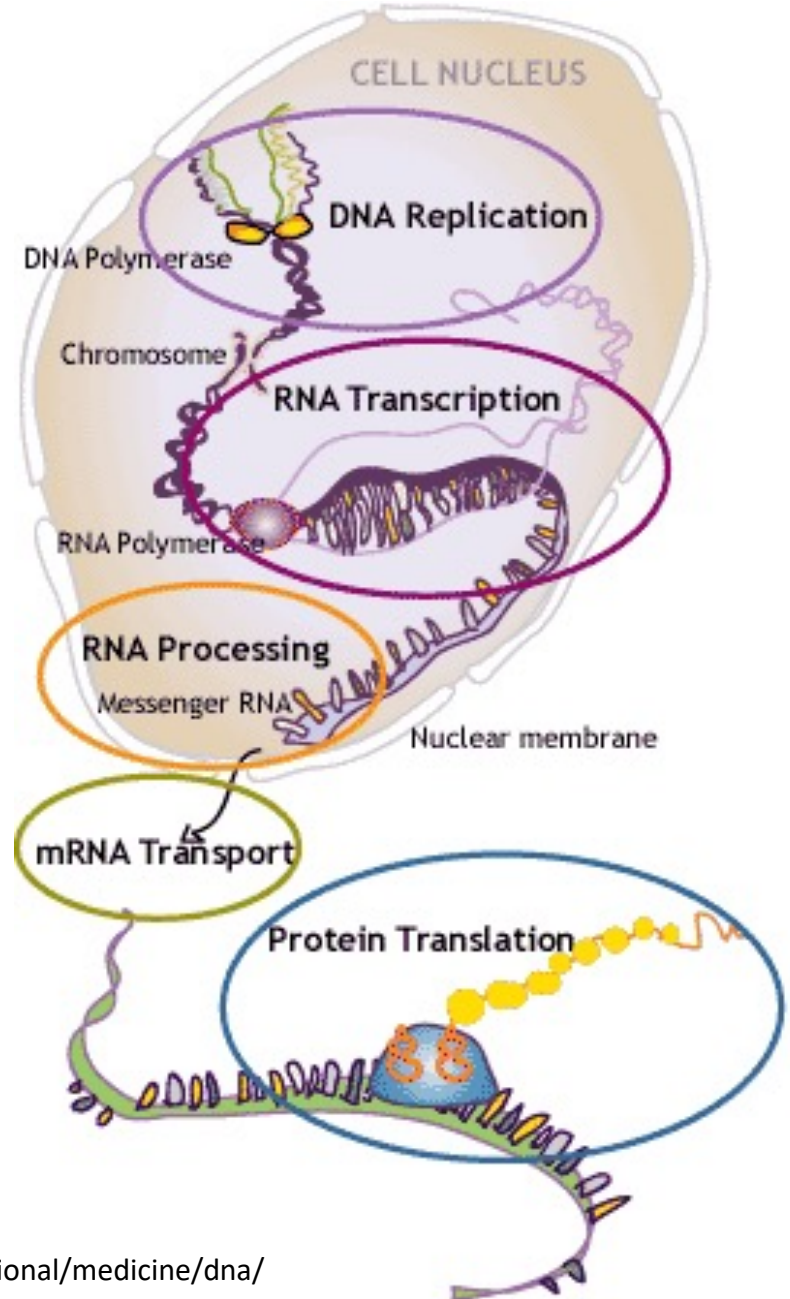
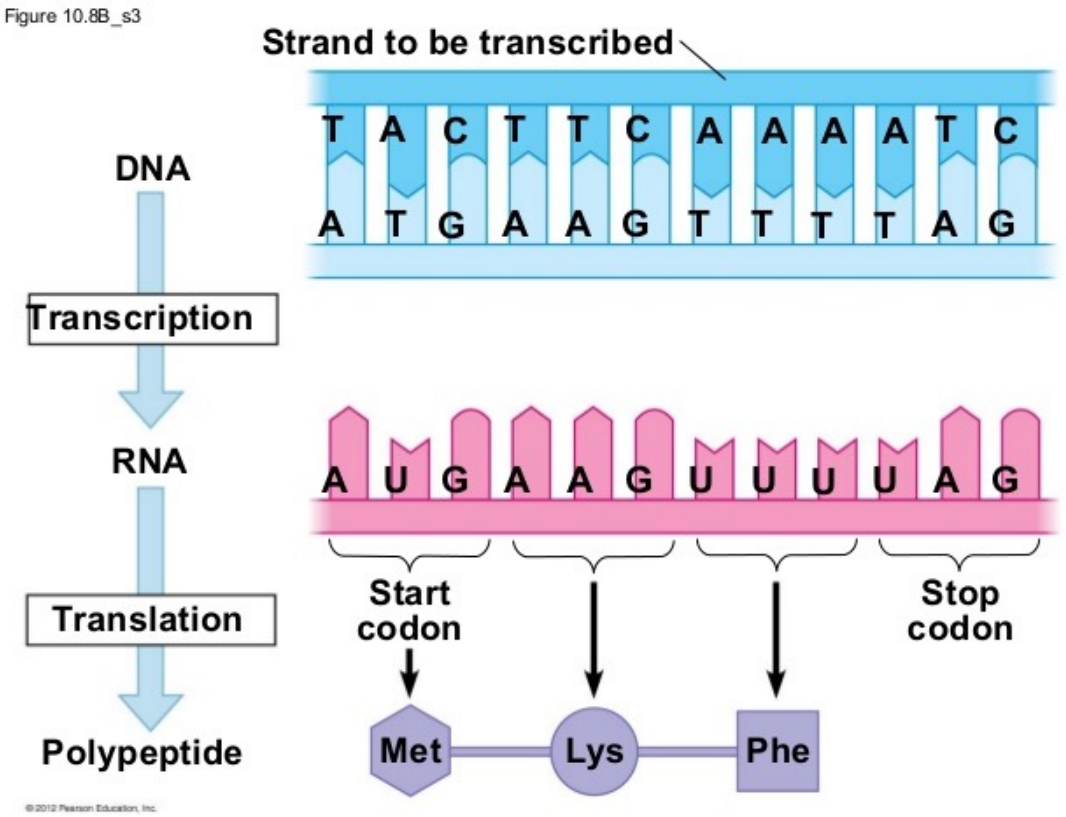
DNA-RNA-Protein



https://www.nobelprize.org/educational/medicine/dna/

Protein Coding



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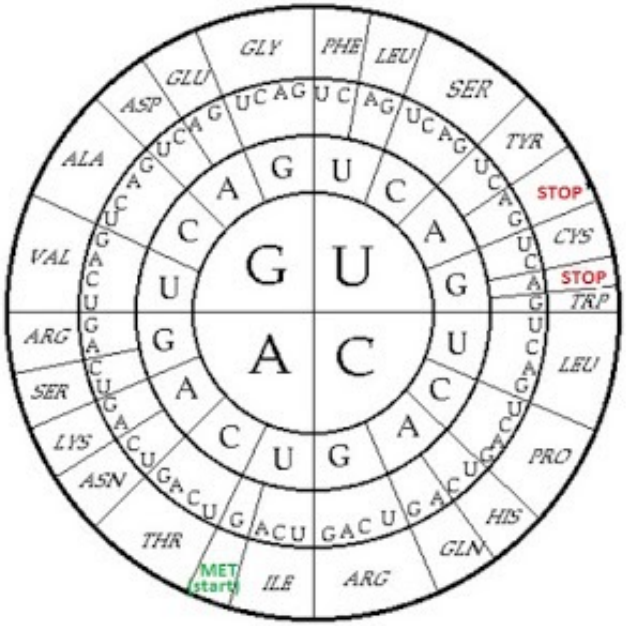

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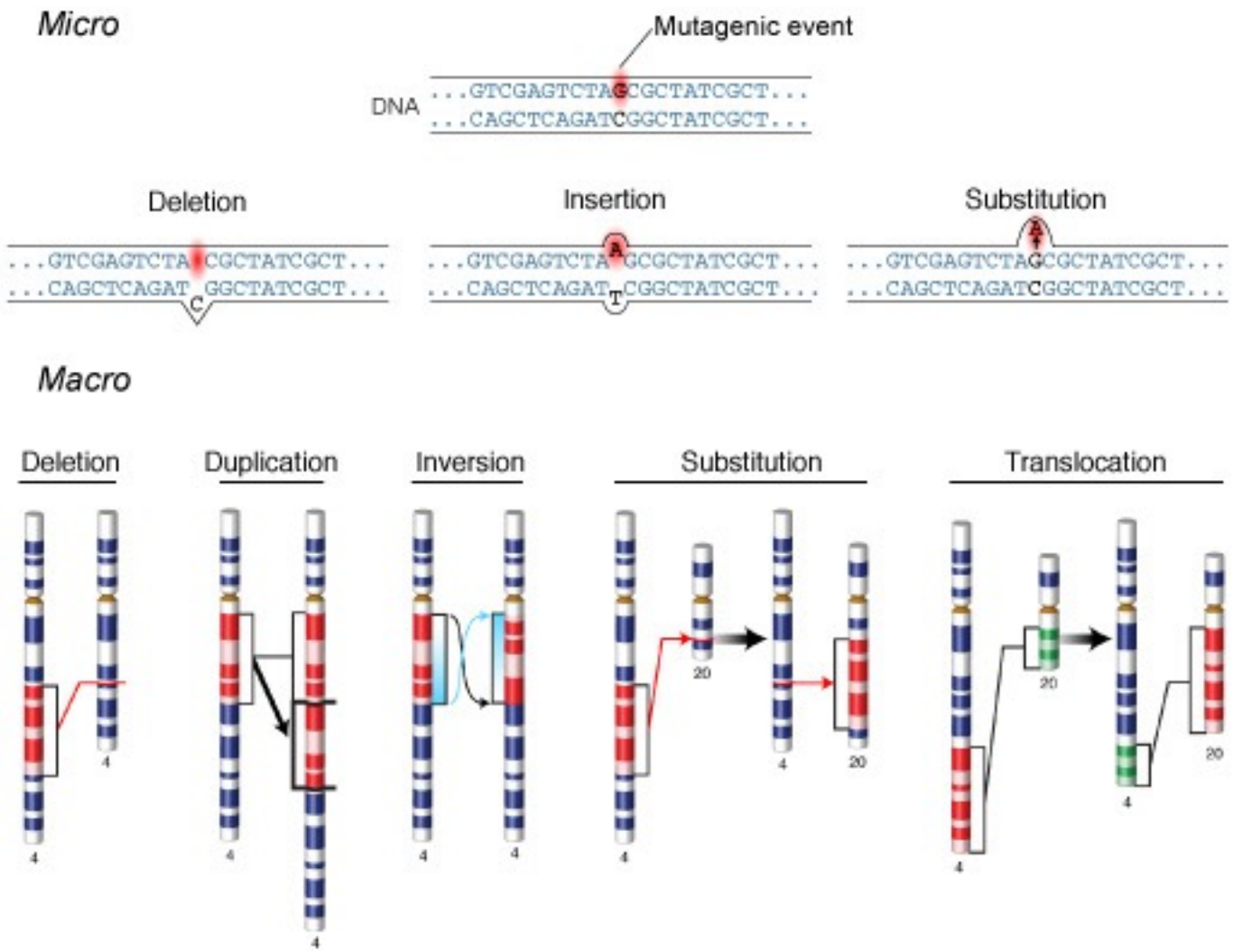
Types of Mutation



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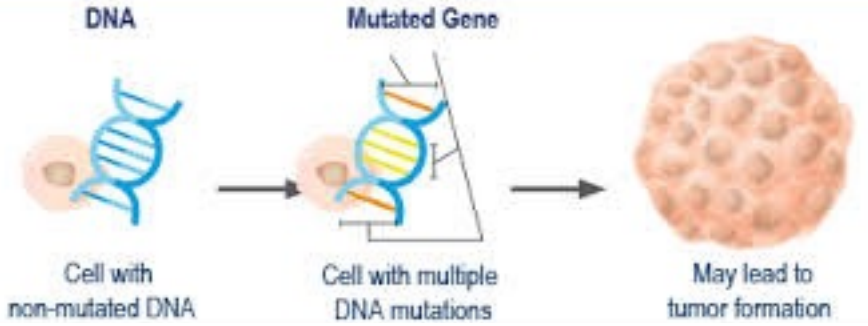
Mutations may lead to cancer



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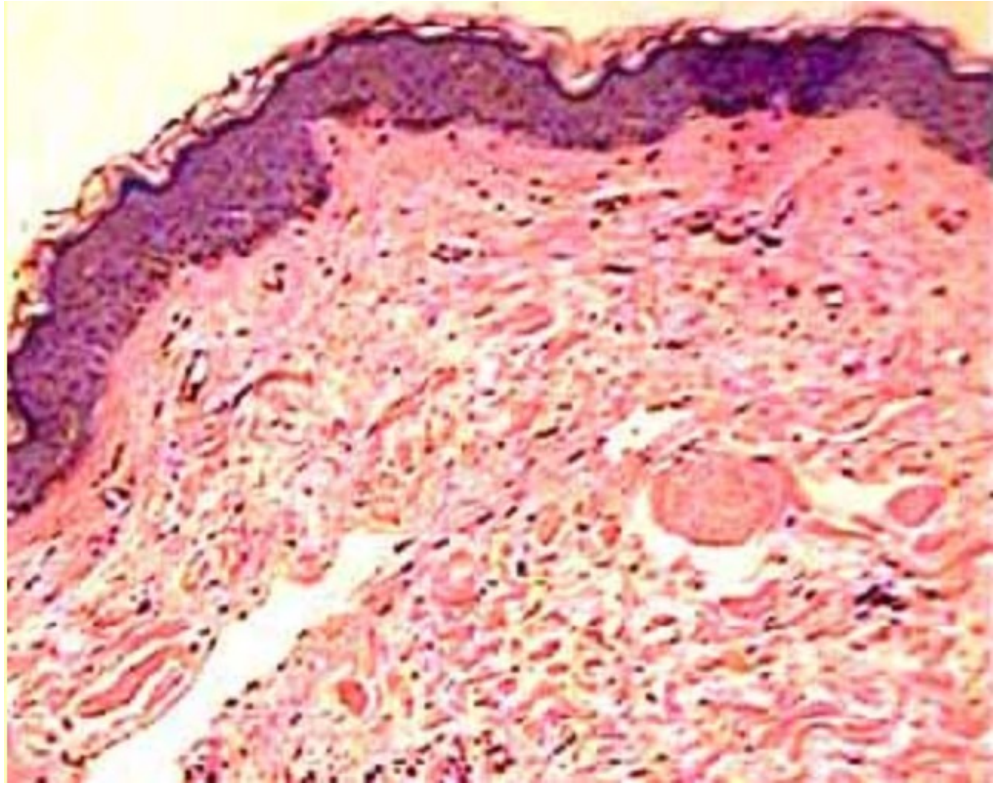
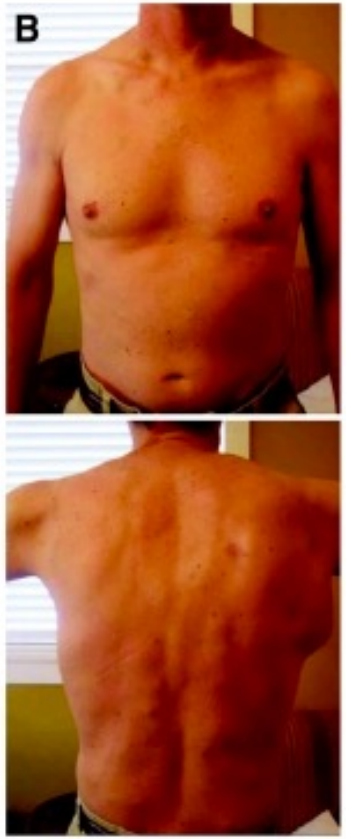
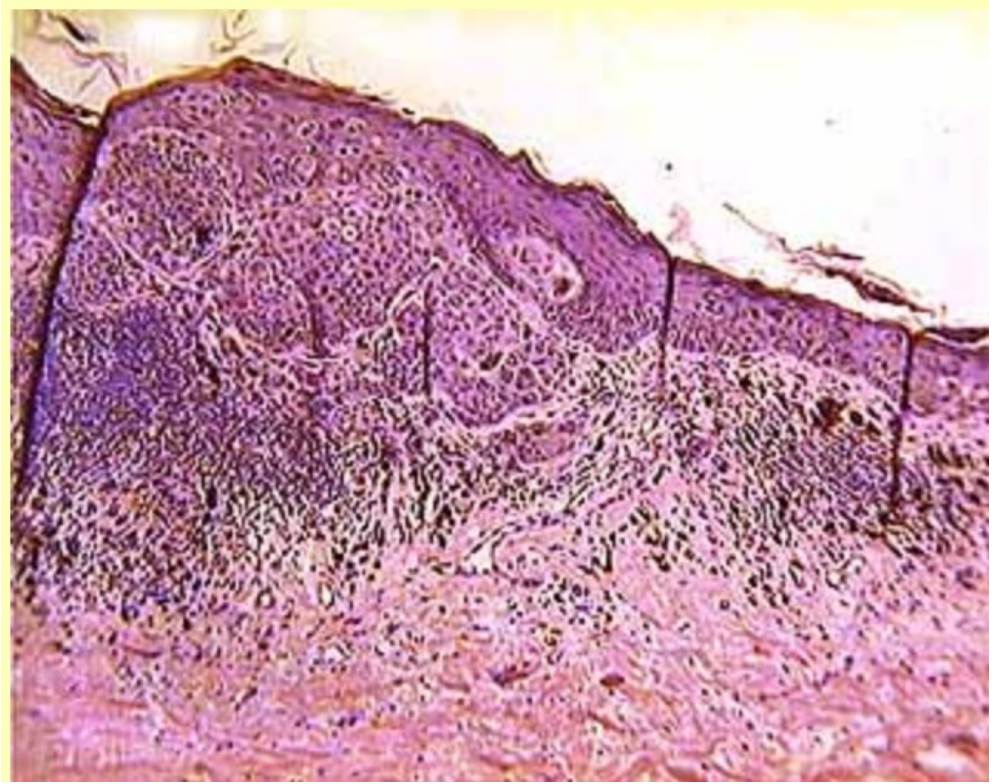
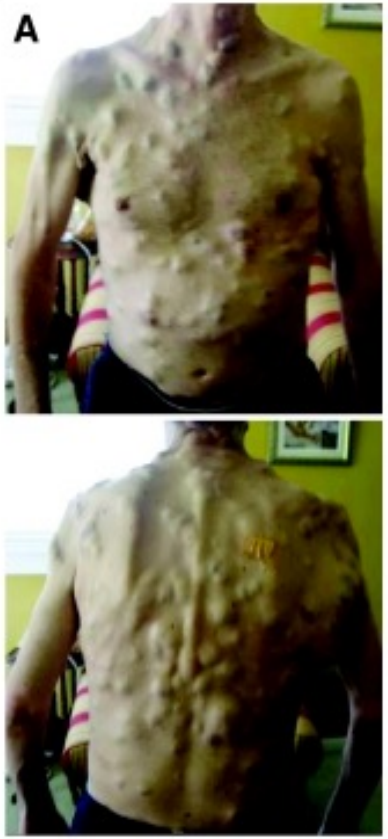
Normal Skin Tissue Under the Microscope





Melanoma Under the Microscope





Mutation of the BRAF gene in the cells of a patient with melanoma

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14], Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

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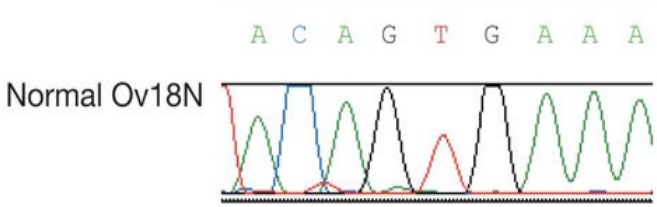

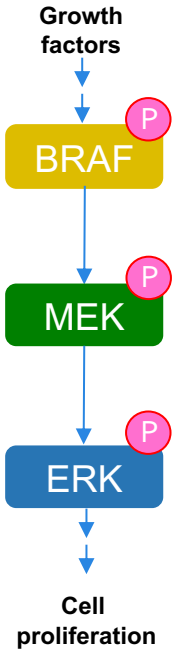

Memorial Sloan Kettering Cancer Center

Mutation of the BRAF gene in the cells of a patient with melanoma

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14], Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

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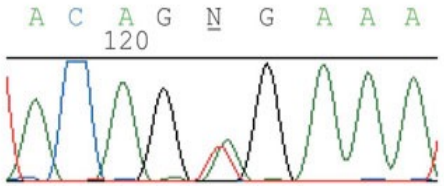
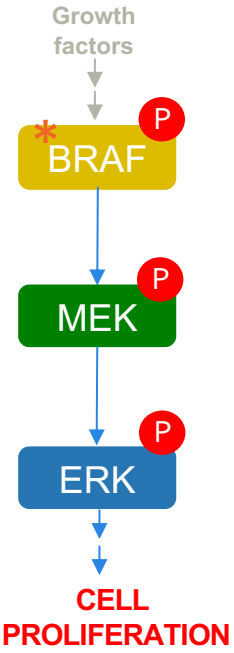
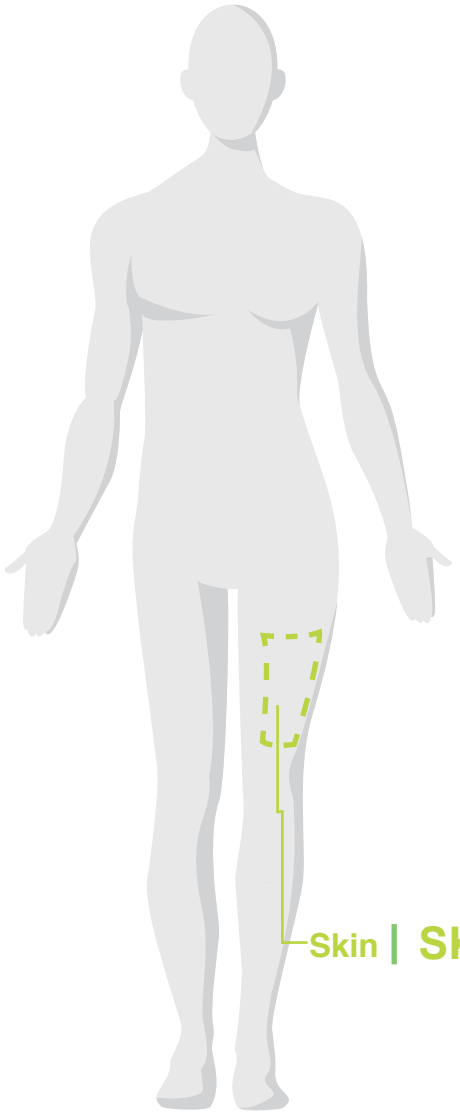
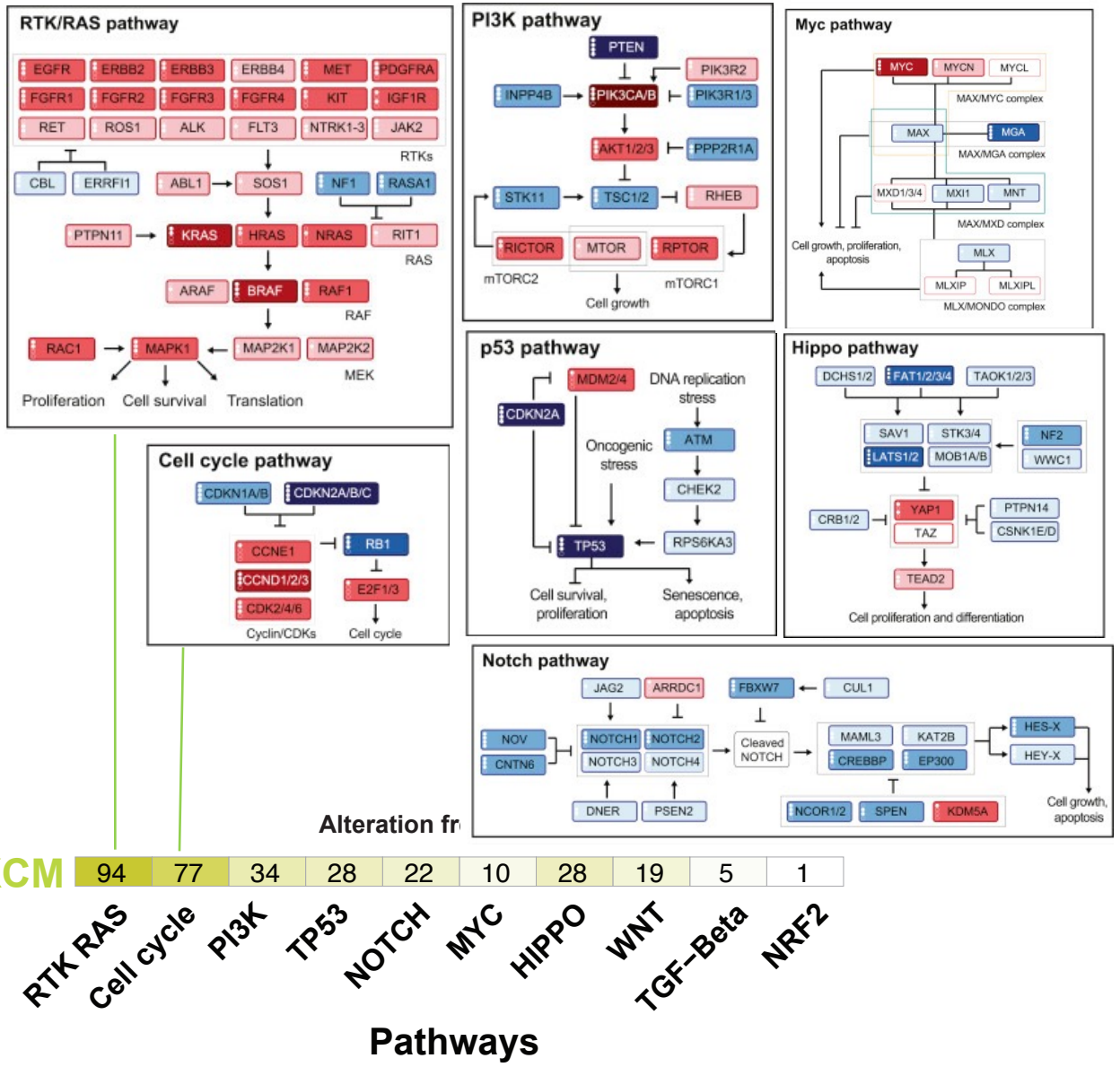




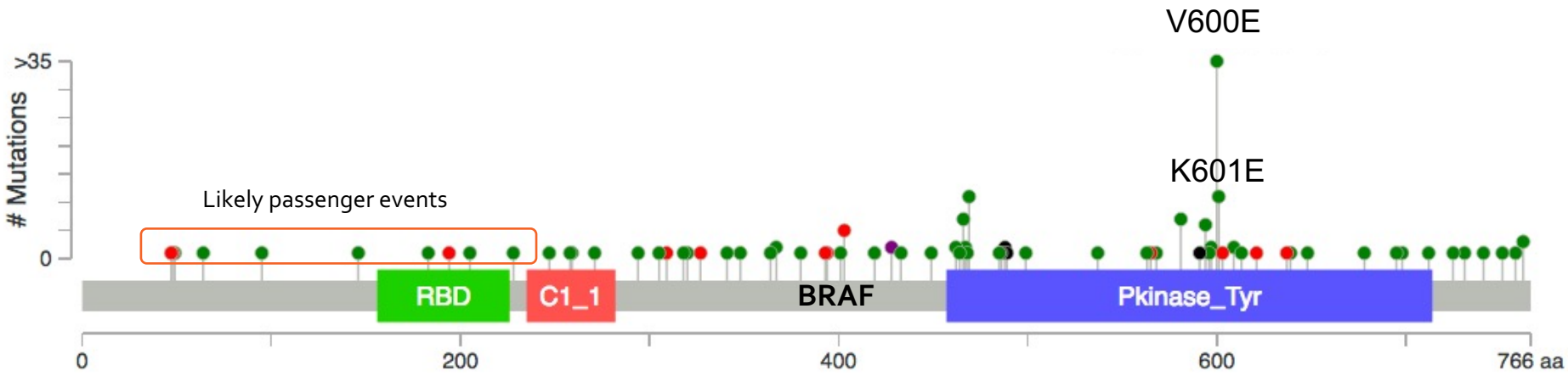
Memorial Sloan Kettering Cancer Center

Different Cancers have different mutations in different pathways

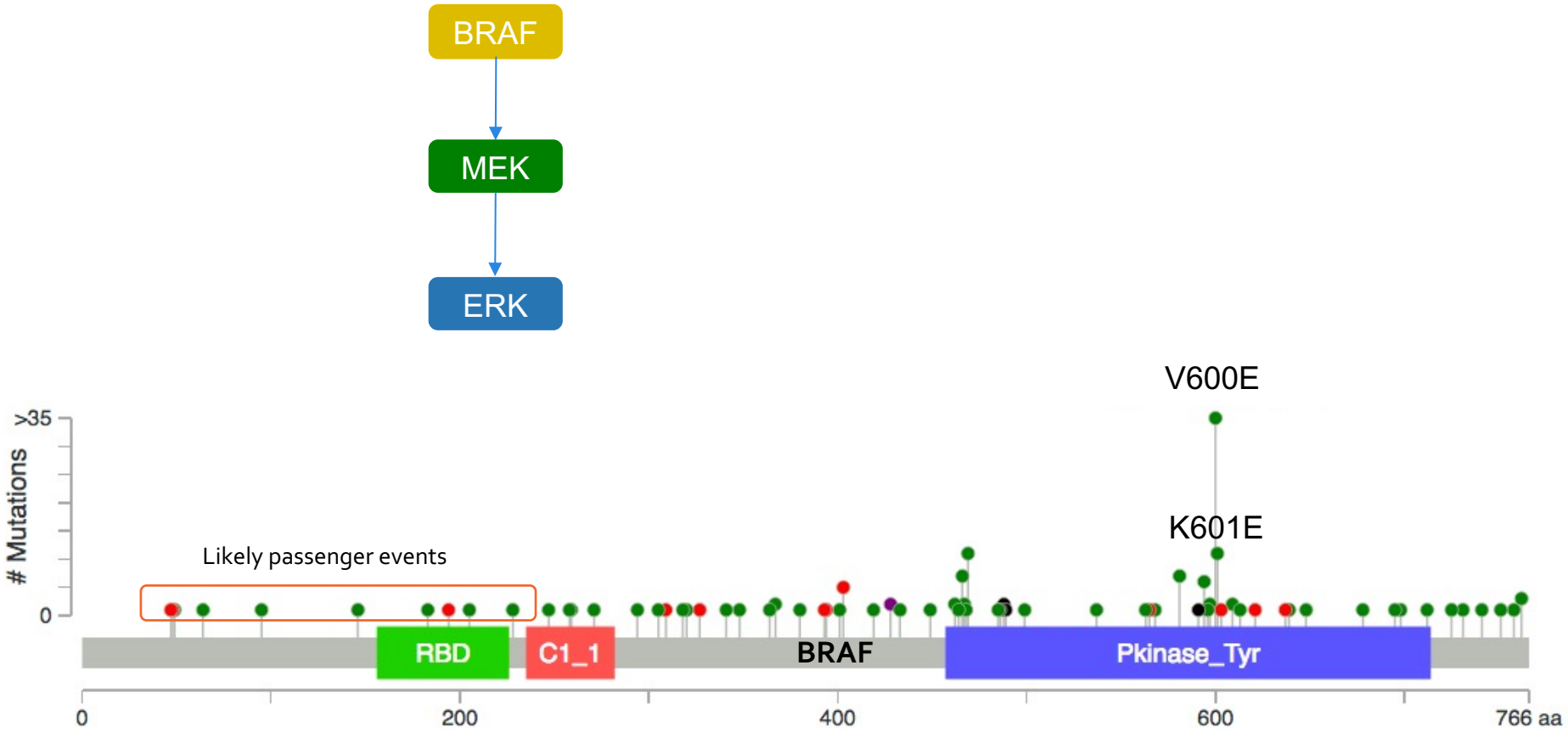




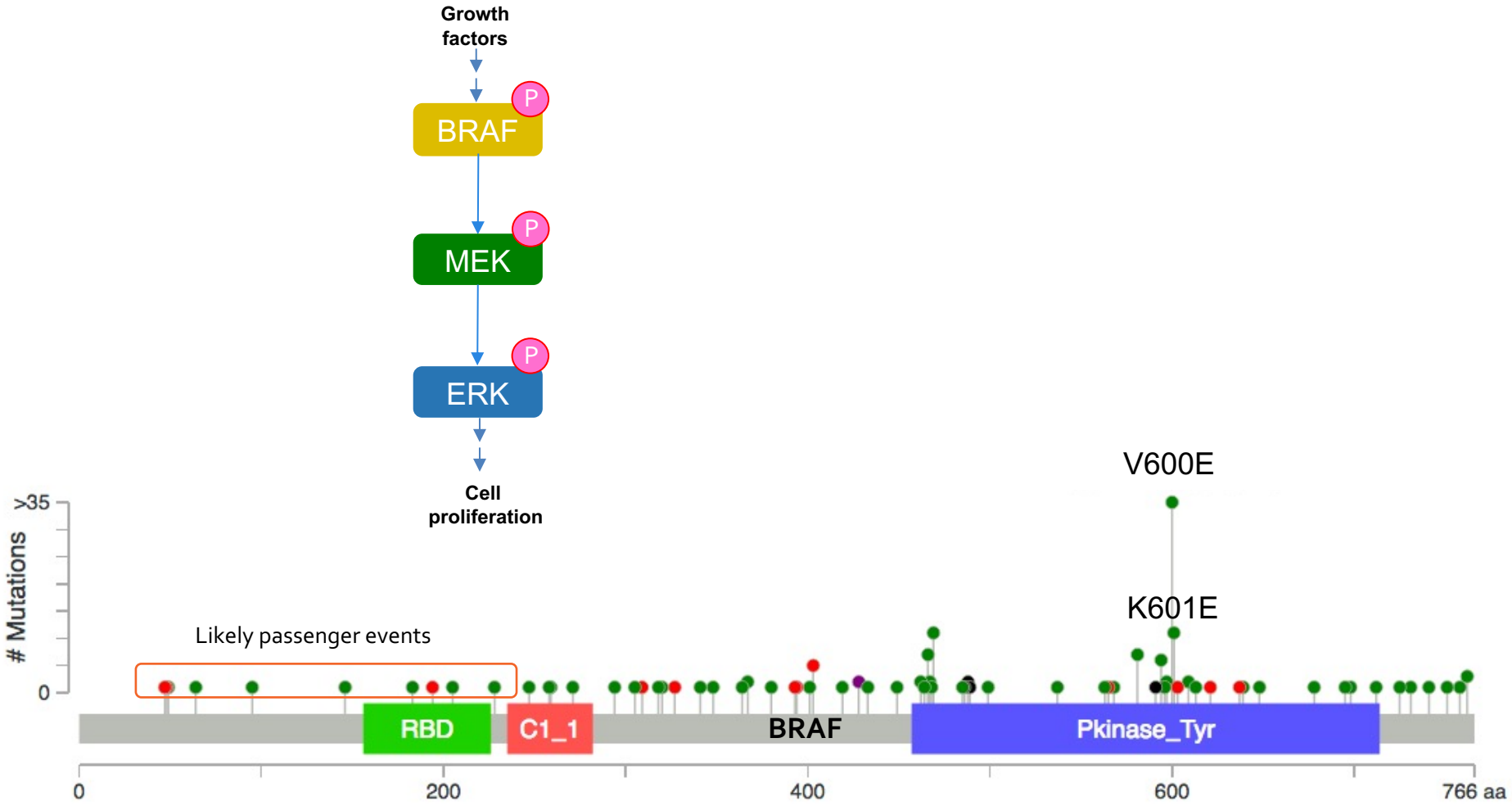
Different mutations have different biochemistries | Example: BRAF



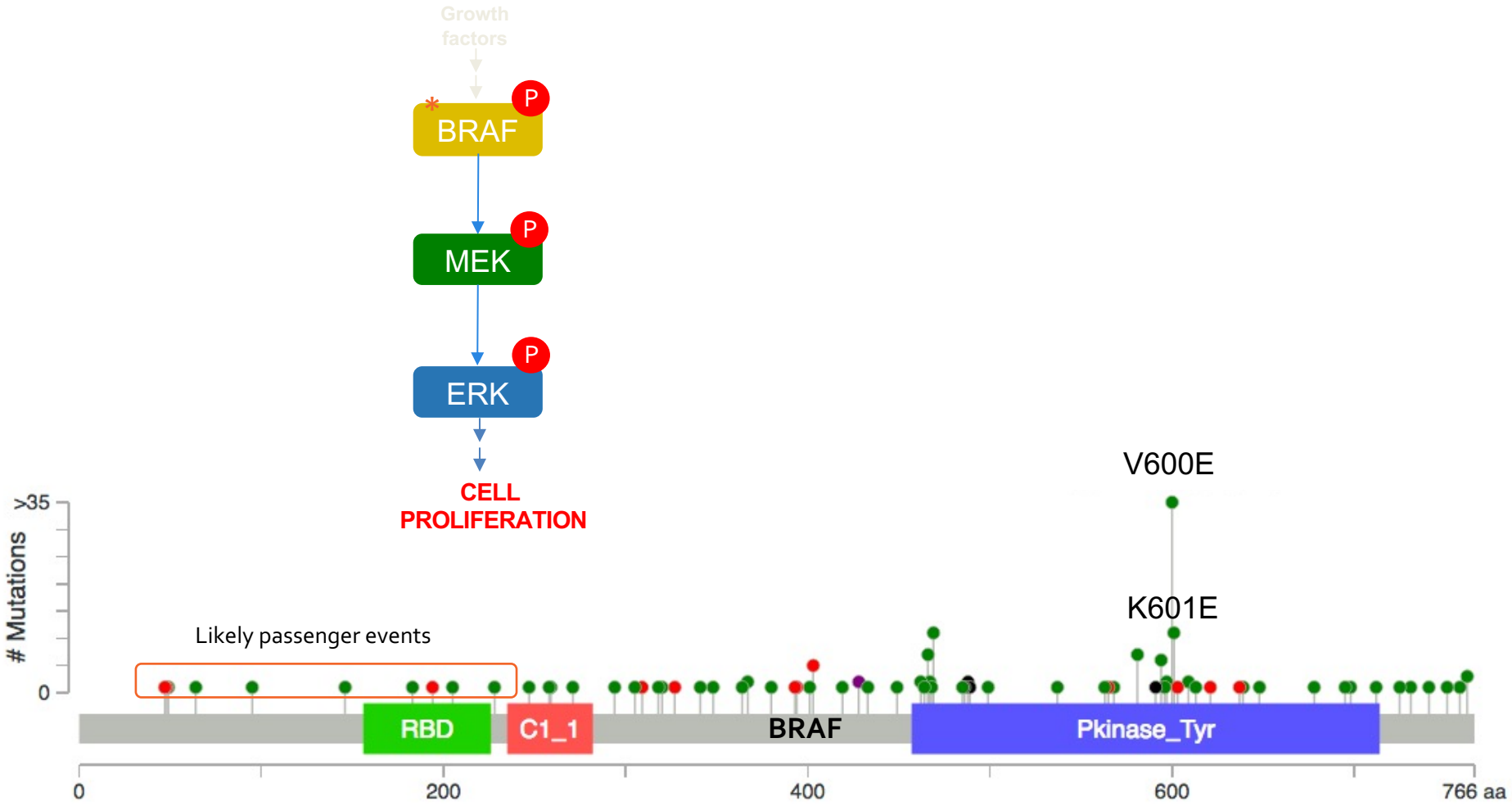
Different mutations have different biochemistries | Example: BRAF



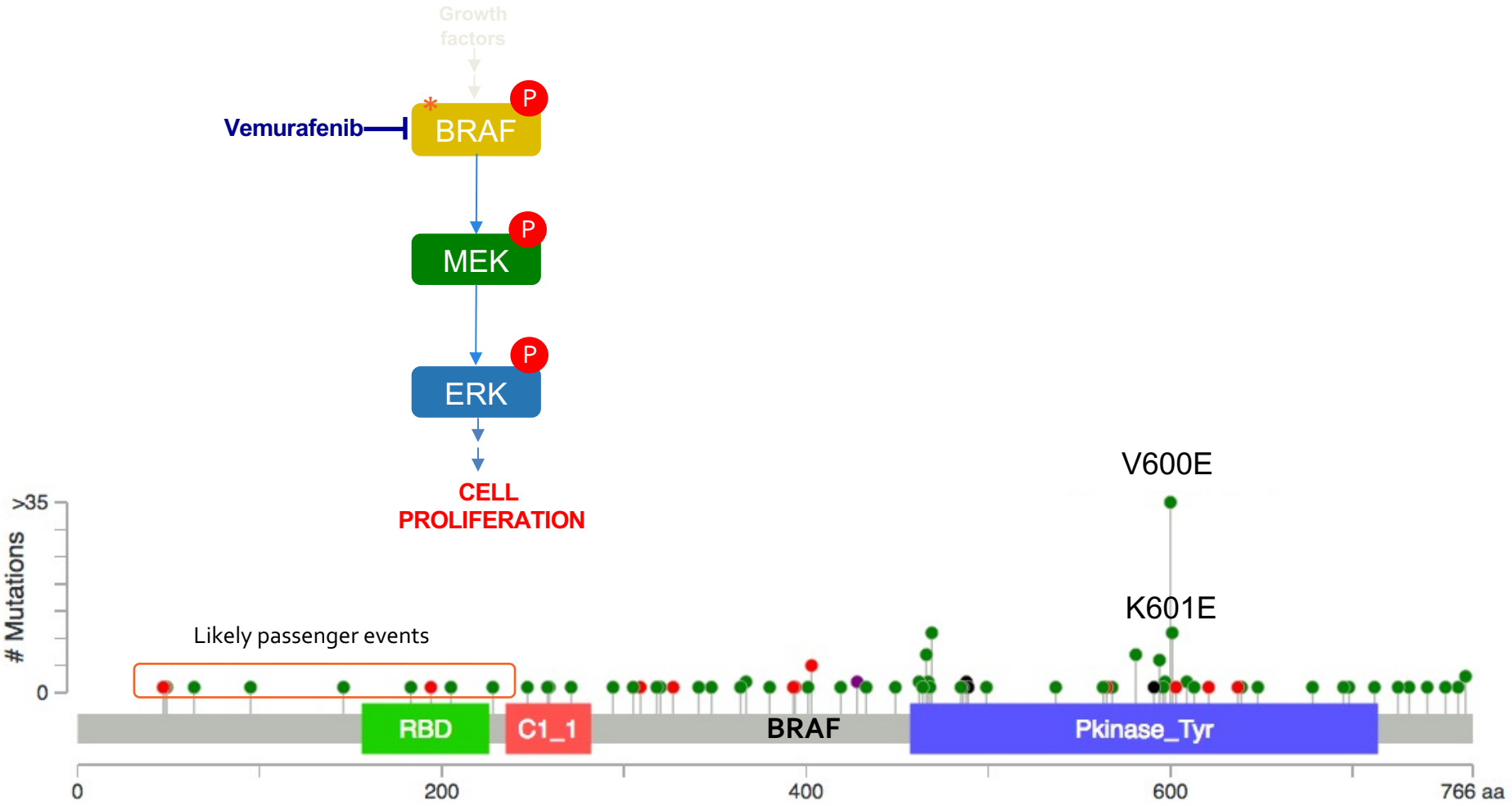
Different mutations have different biochemistries | Example: BRAF



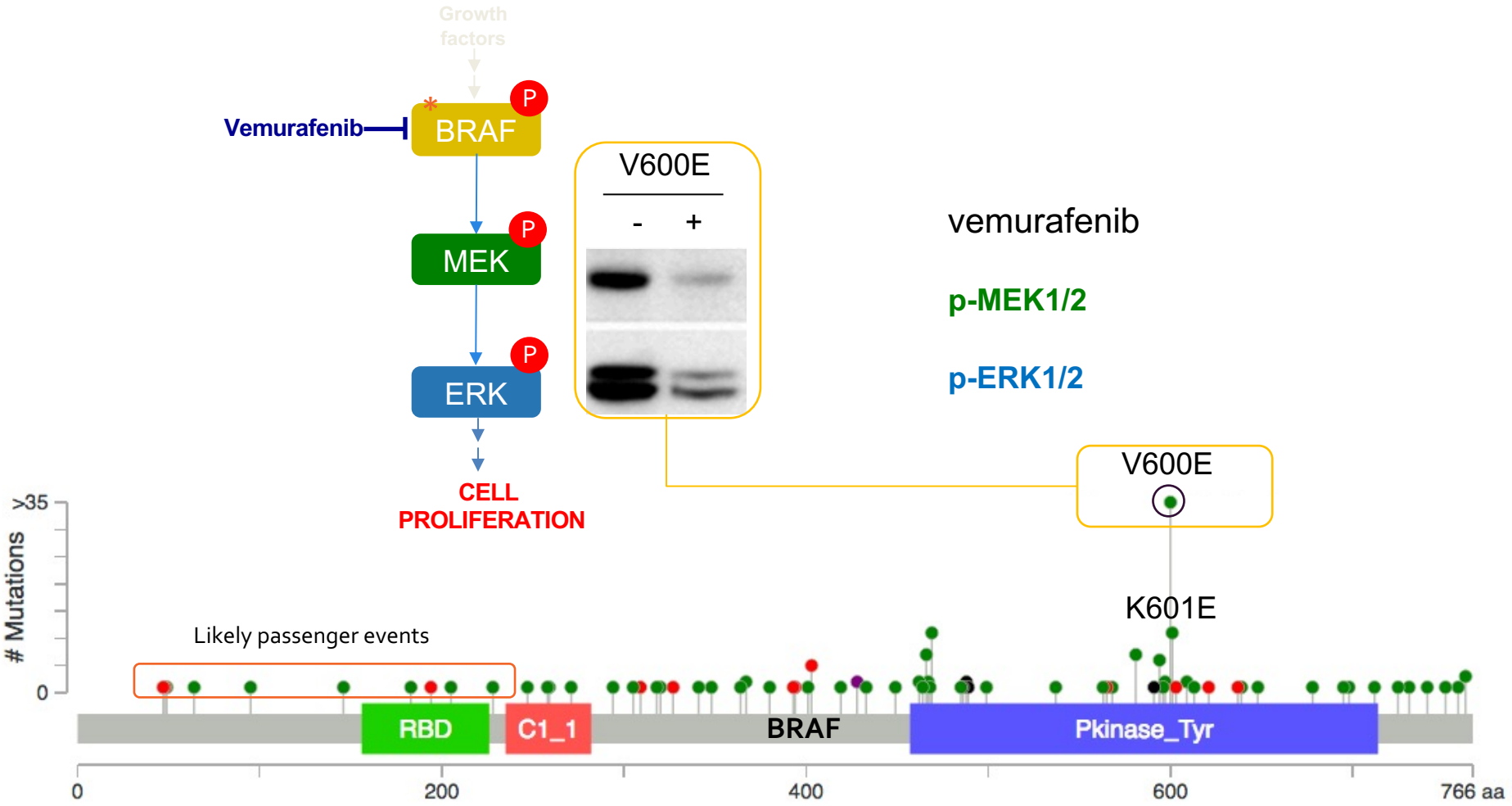
Different mutations have different biochemistries | Example: BRAF



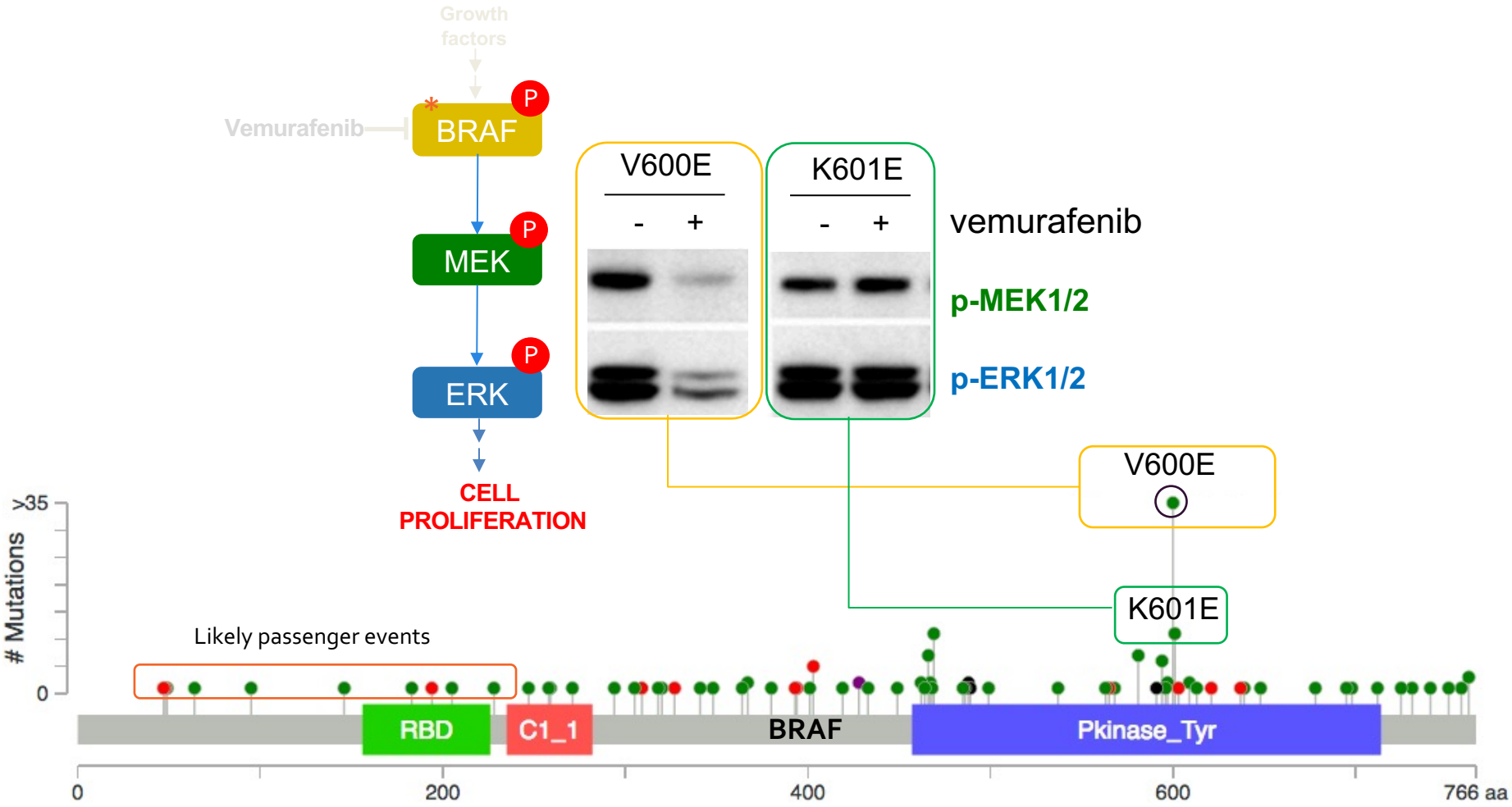
Different mutations have different biochemistries | Example: BRAF



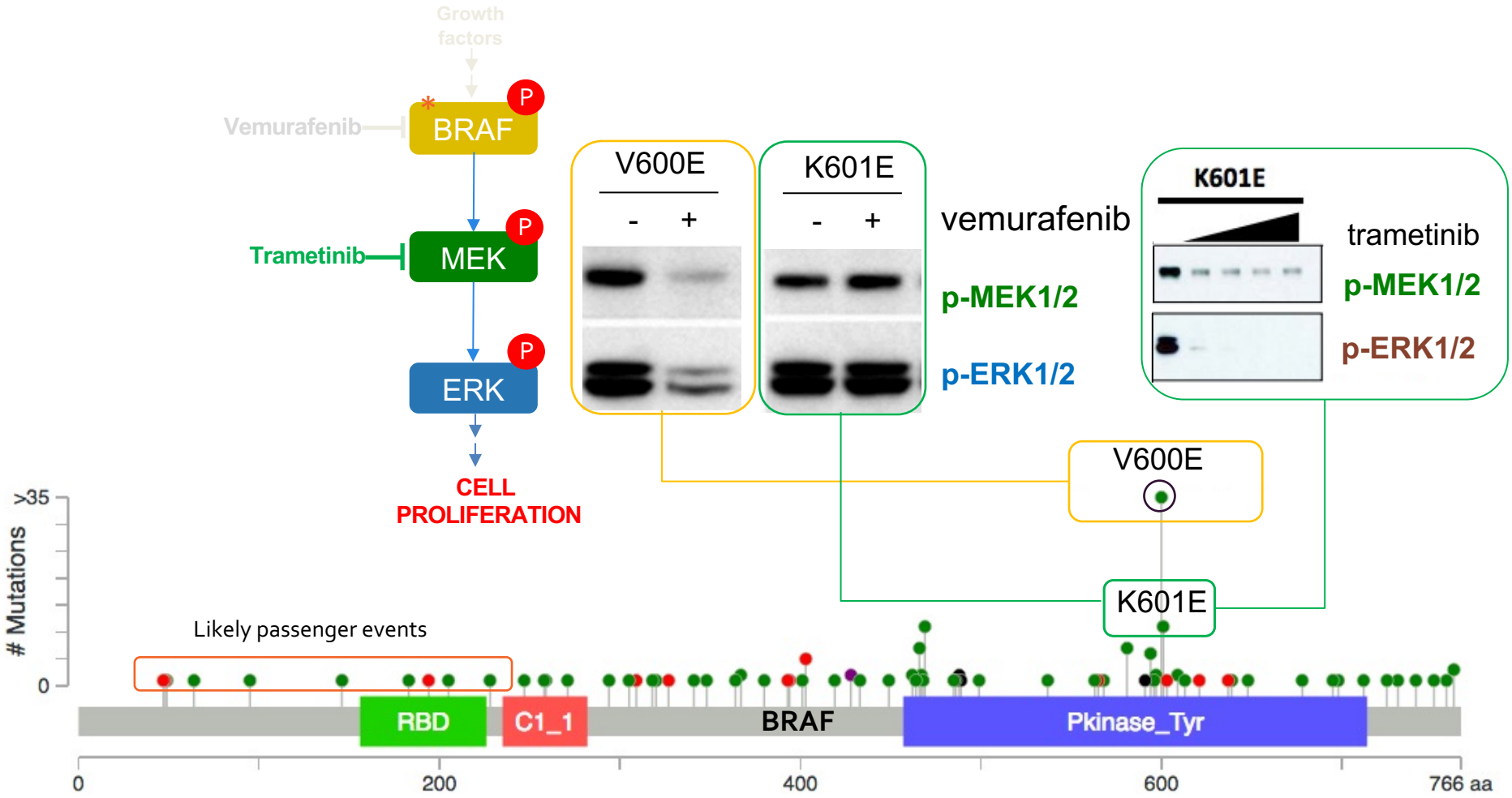
Different mutations have different biochemistries | Example: BRAF



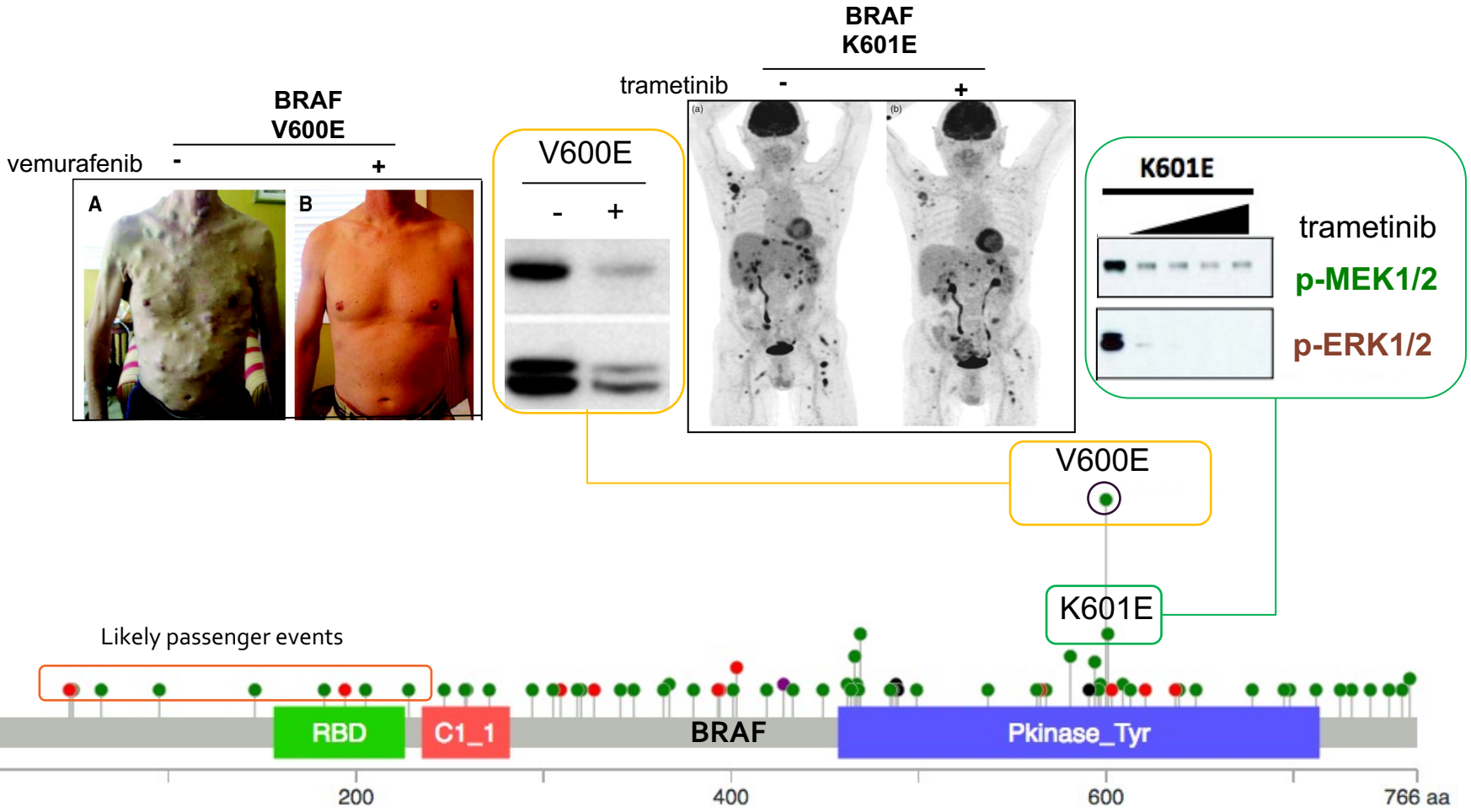
Different mutations have different biochemistries | Example: BRAF



Different mutations have different biochemistries | Example: BRAF

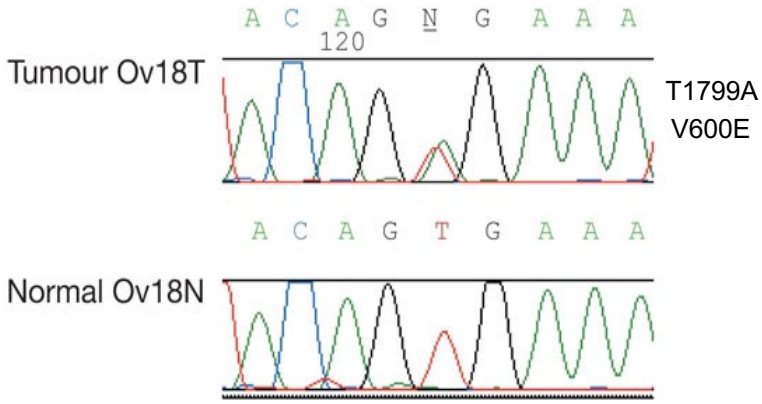


Different mutations have different biochemistries | Example: BRAF

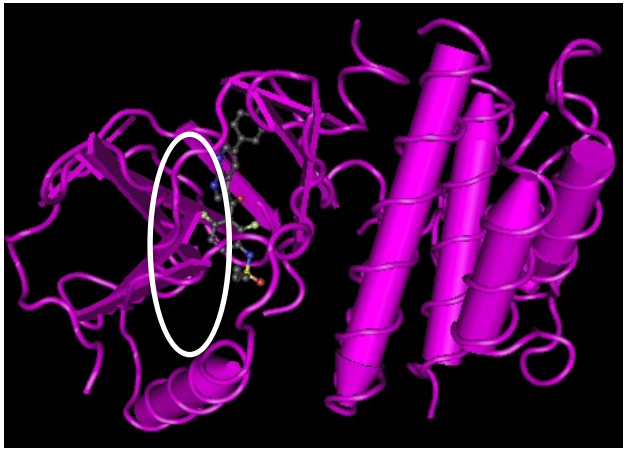


From sequencing to drug to treatment

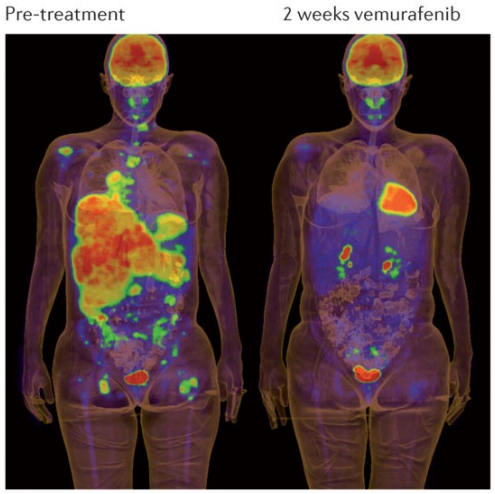
DNA Sequencing →
Discovery of a driver mutation
BRAF V600E

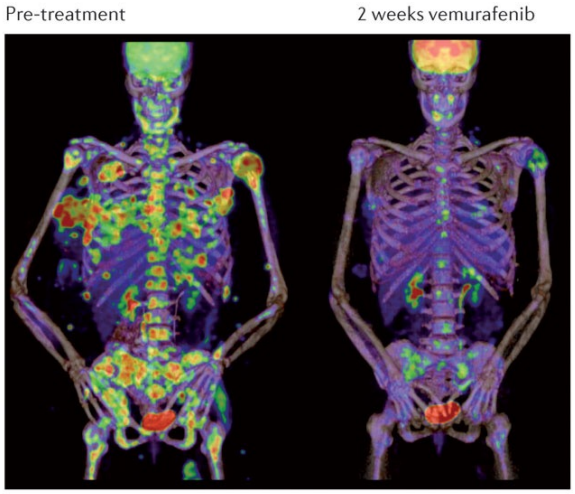


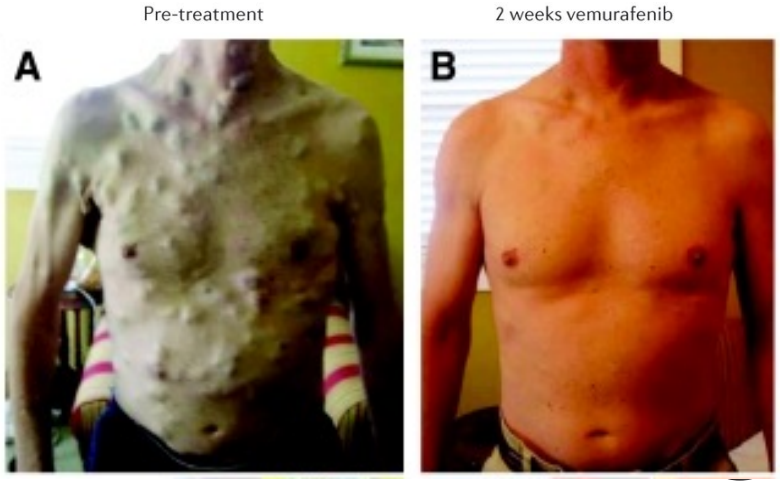
Drug Development →
Inhibits the mutant protein
Vemurafenib



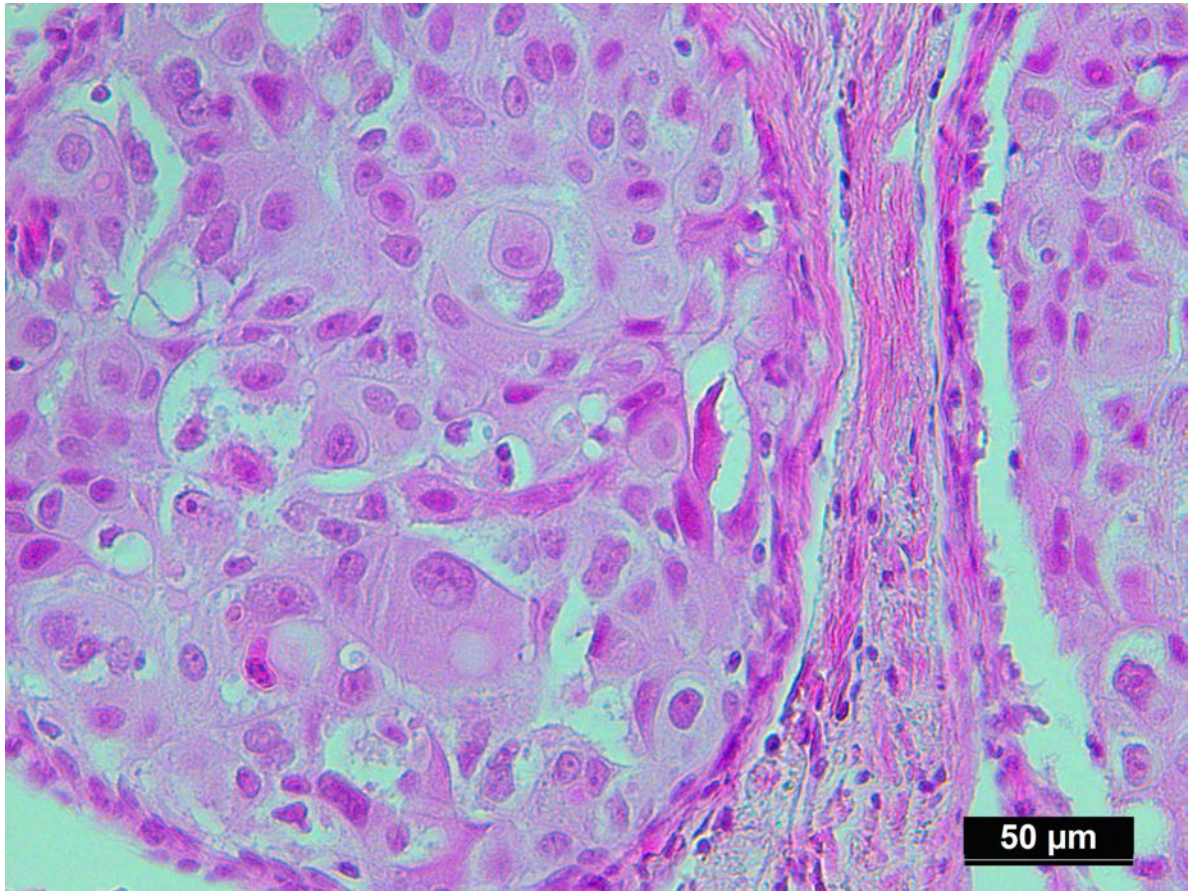
Changes in Clinical Practice



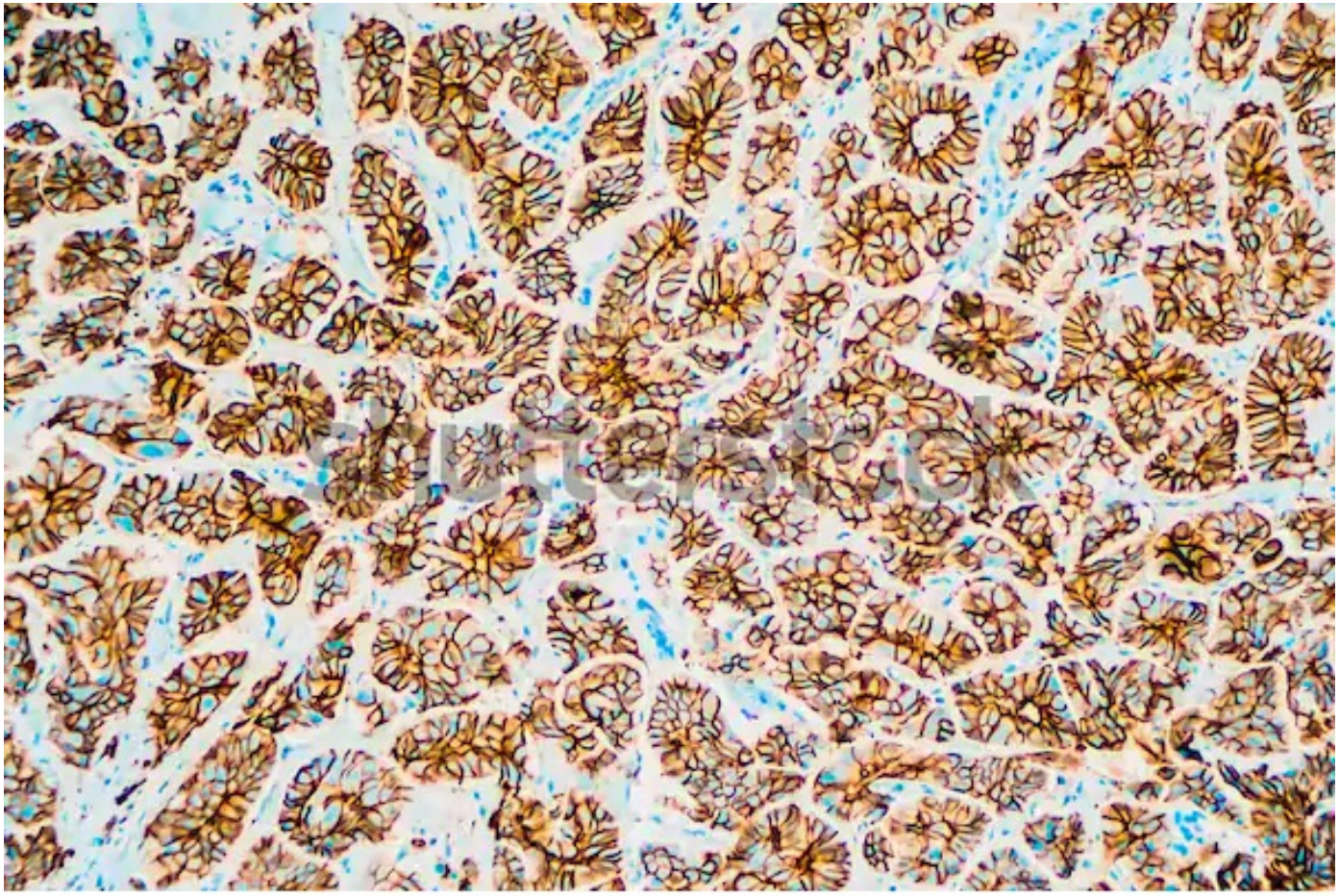




Normal Breast Tissue Under the microscope



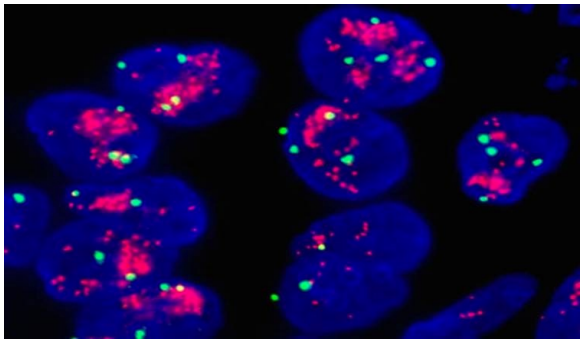
HER2-Amplified Breast Cancer Under a Microscope



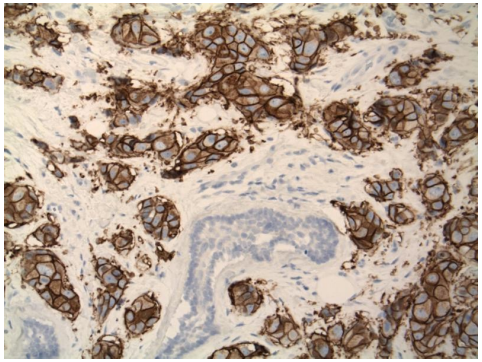
The first targeted therapy was anti-HER2 tx in breast cancer

20-25% of invasive breast cancers overexpress HER2
HER2 overexpression promotes cell proliferation and survival

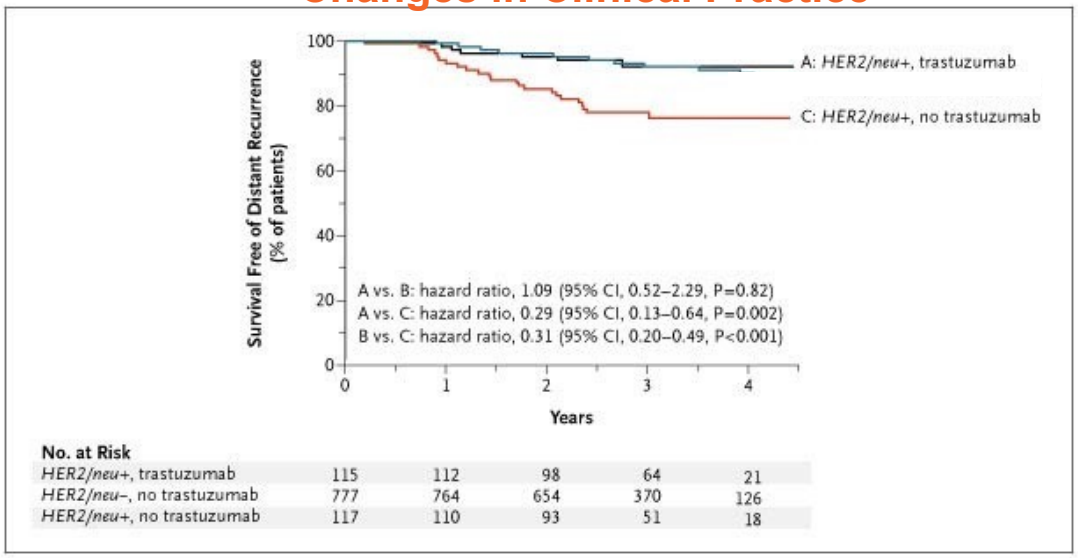
DNA Sequencing → Discovery of a driver mutation
ERBB2 amplification



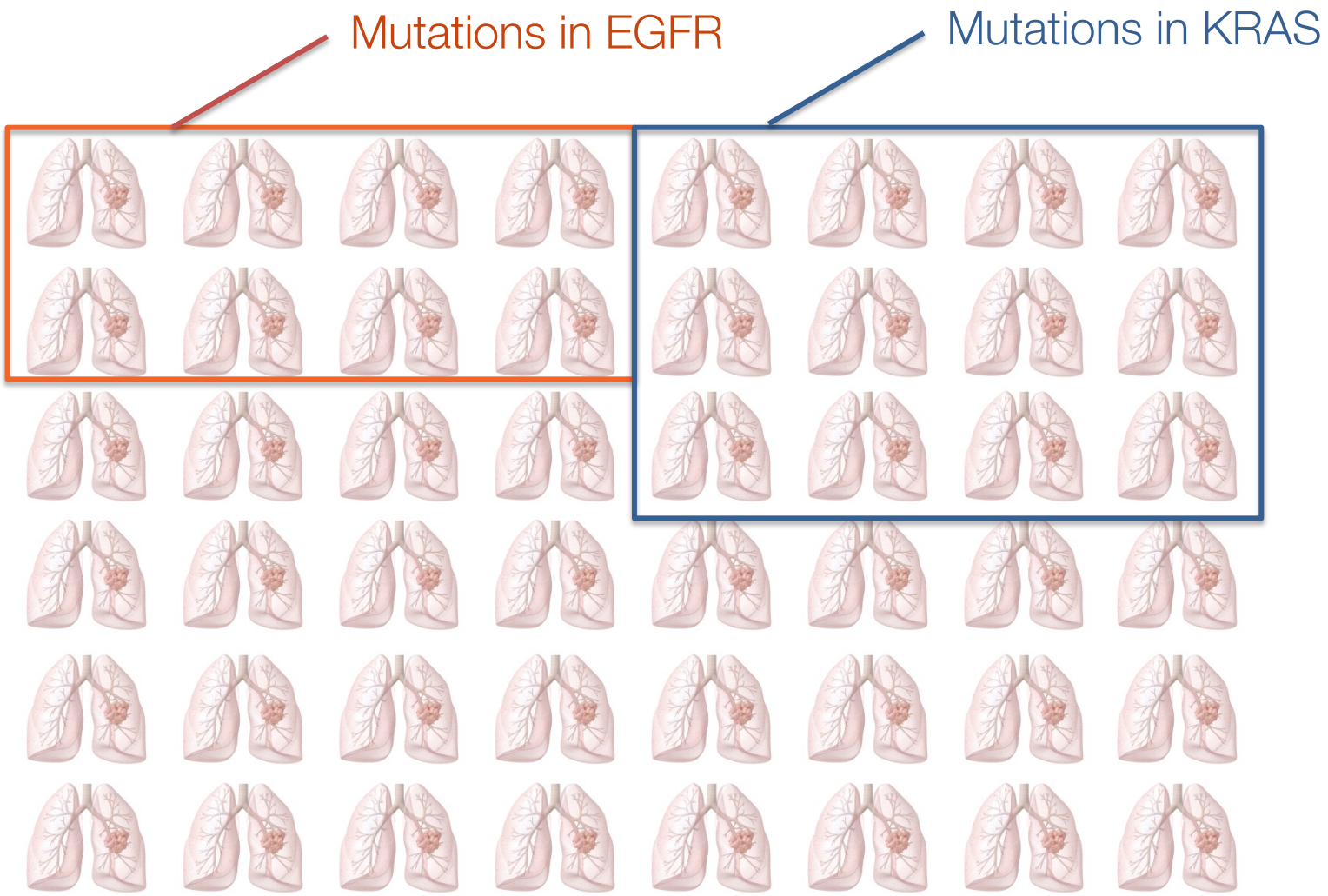
Protein → Overexpression of the HER2 protein



Changes in Clinical Practice



Precision Oncology

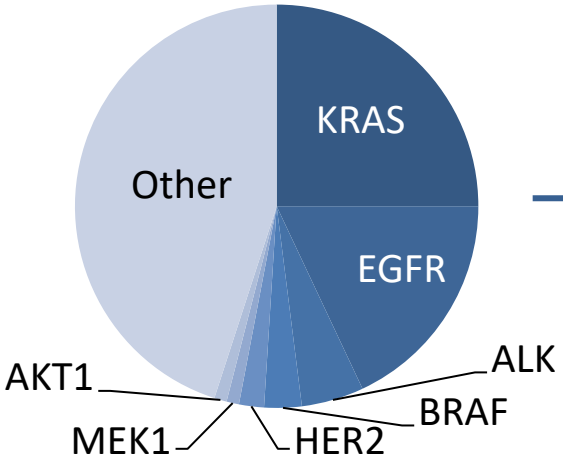


Cancer is a disease of the genome

Michael Berger

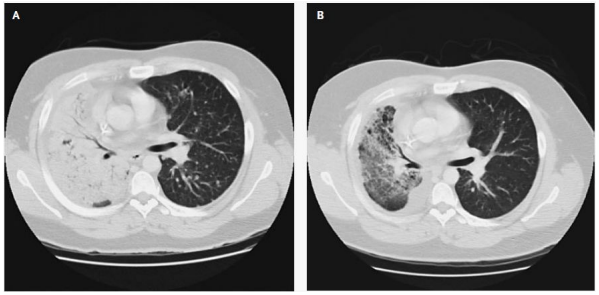
Precision Oncology

Lung Cancer



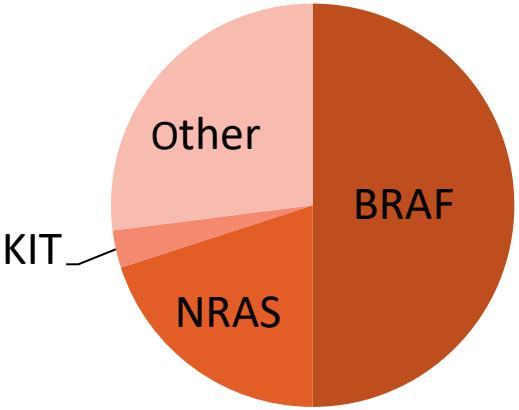
EGFR-mutant cancer

EGFR inhibitors:
erlotinib, gefinitib



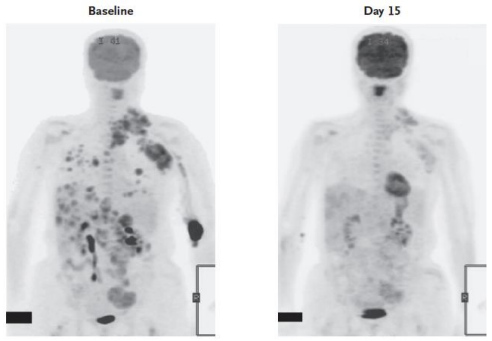
Lynch et al., NEJM, 2004
Paez et al., Science, 2004
Pao et al., PNAS, 2004

Melanoma



BRAF-mutant cancer

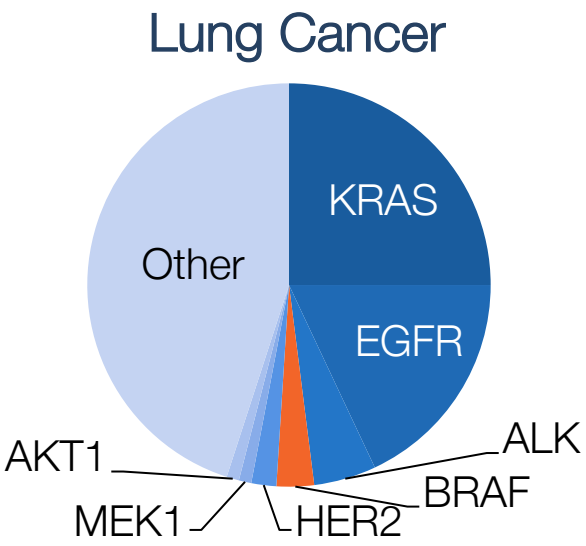
BRAF inhibitor:
vemurafenib, dabrafenib



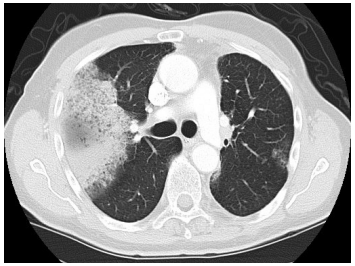
Flaherty et al., NEJM, 2010

Michael Berger

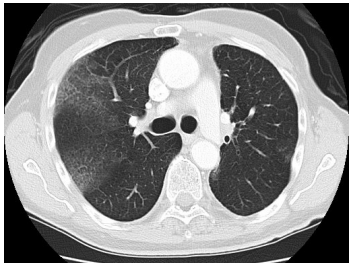
Precision Oncology



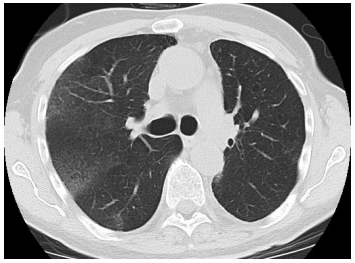
Response to Dabrafenib



Baseline



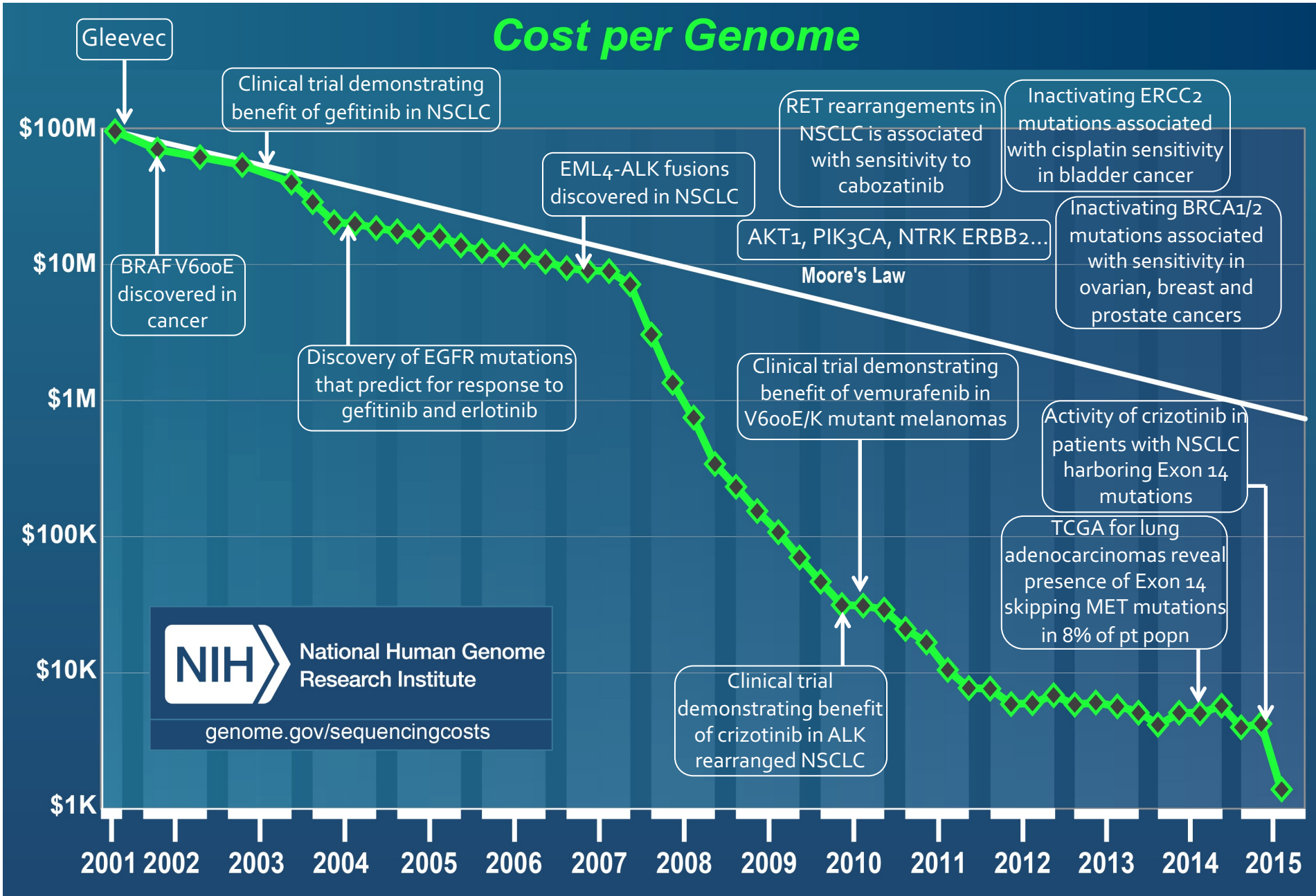
6 weeks on Dabrafenib



4 months on Dabrafenib

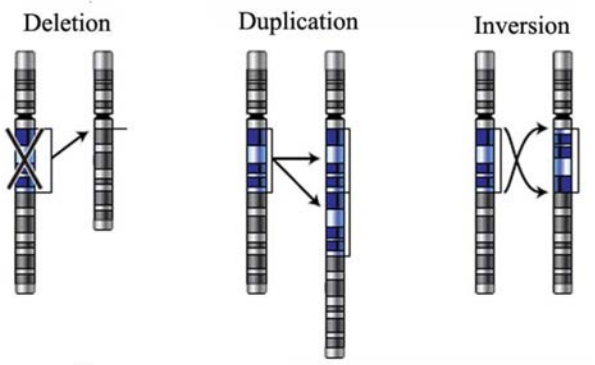
Courtesy Dr. Greg Riely

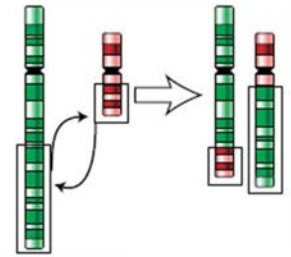
A Timeline of Targeted Therapies



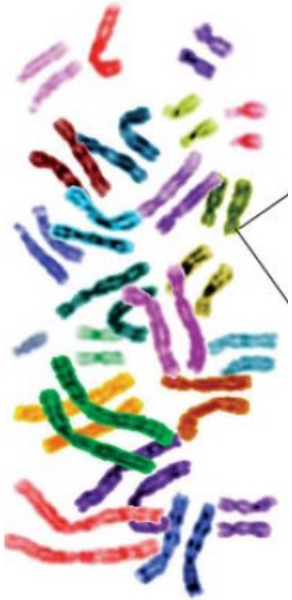
Types of Mutations

Chromosomal

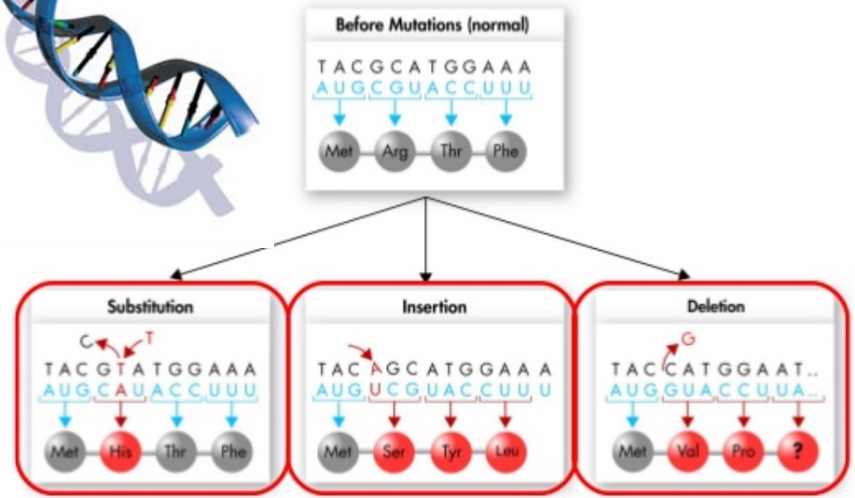




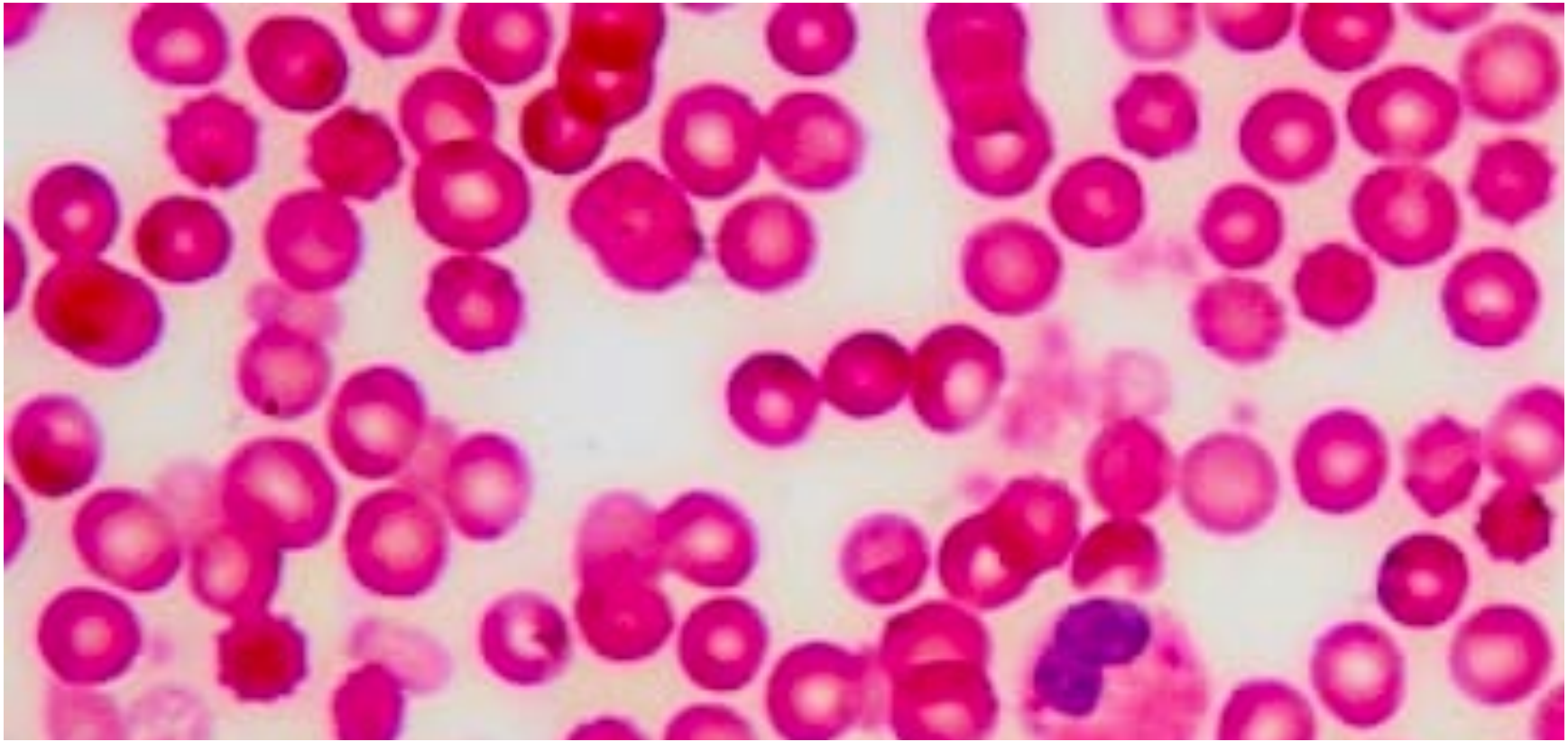
Reciprocal Translocation



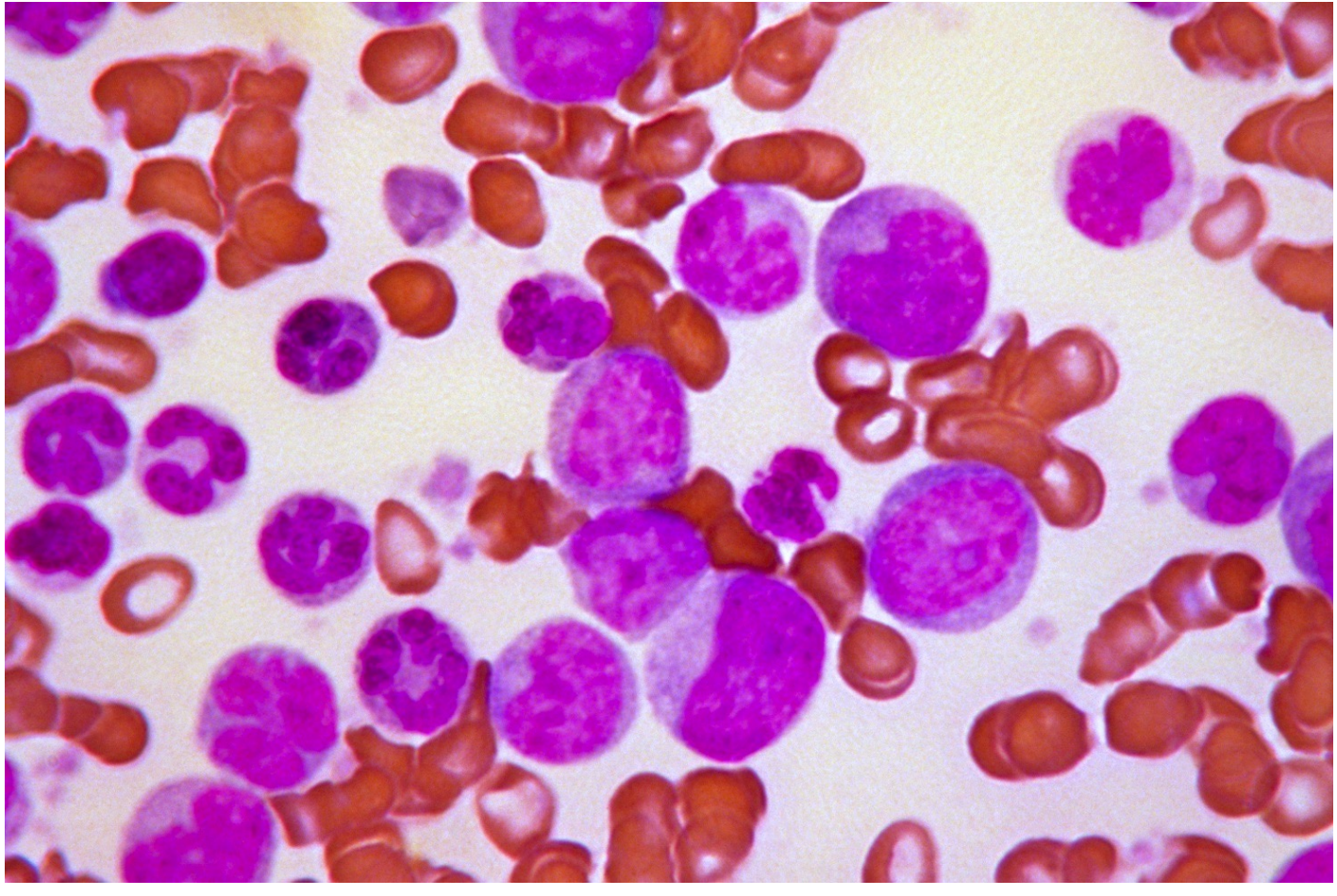
Point Mutations



Normal Blood Under a Microscope



Blood of Patients with Chronic Myeloid Leukemia



Chromosomes 9 and 22 in blood cells of a patient with CML

A Minute Chromosome in Human Chronic Granulocytic Leukemia

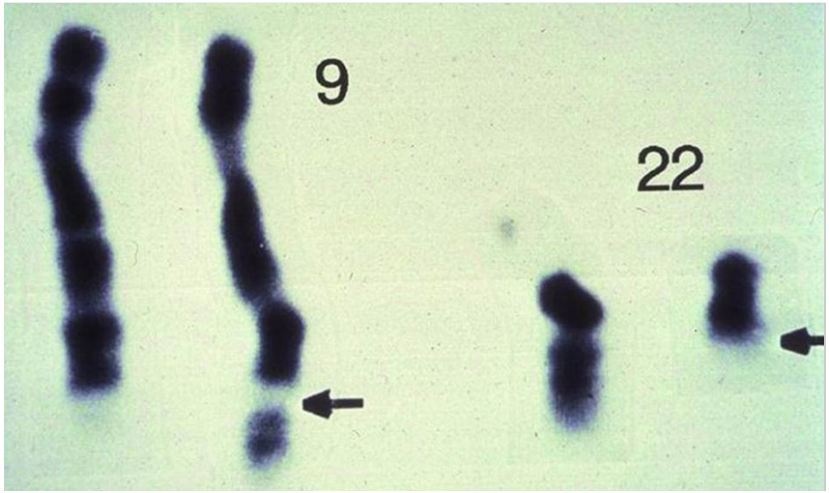
In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* 25, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
School of Medicine, University of Pennsylvania
DAVID A. HUNGERFORD
Institute for Cancer Research

Nowell & Hungerford, 1960 Science 132.1497



Amplification of the ERBB2 gene cells of a patient with HER2+ breast cancer

Amplification of a Novel v-*erbB*–Related Gene in a Human Mammary Carcinoma

C. Richter King
Matthias H. Kraus
Stuart A. Aaronson
Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, Maryland 20205

certain human tumors (6) or tumor cell lines (7). We now report the detection and partial isolation of a gene that is a new member of the tyrosine kinase family and is amplified in a human mammary carcinoma. This gene is closely related

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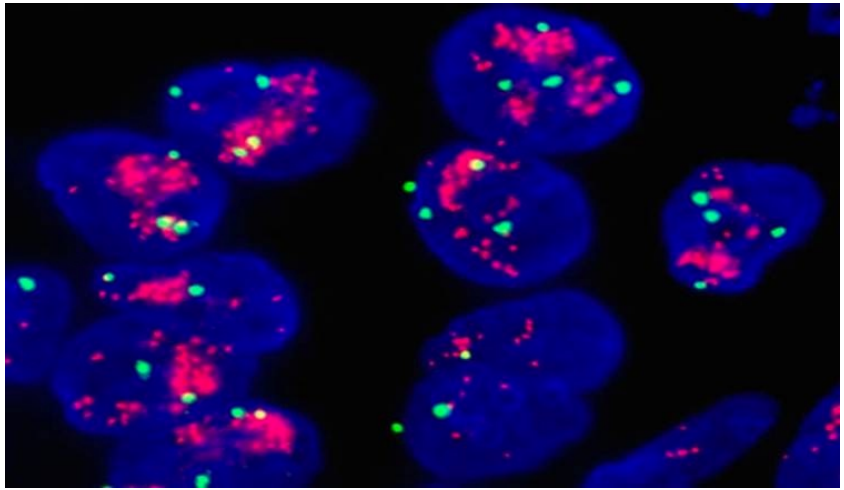
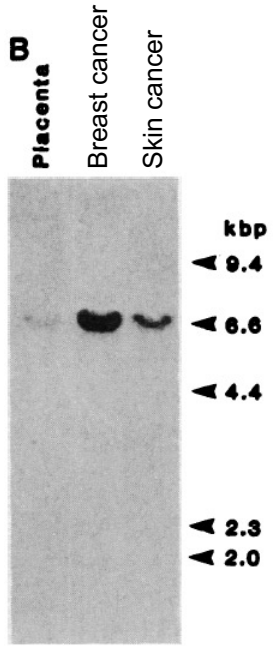
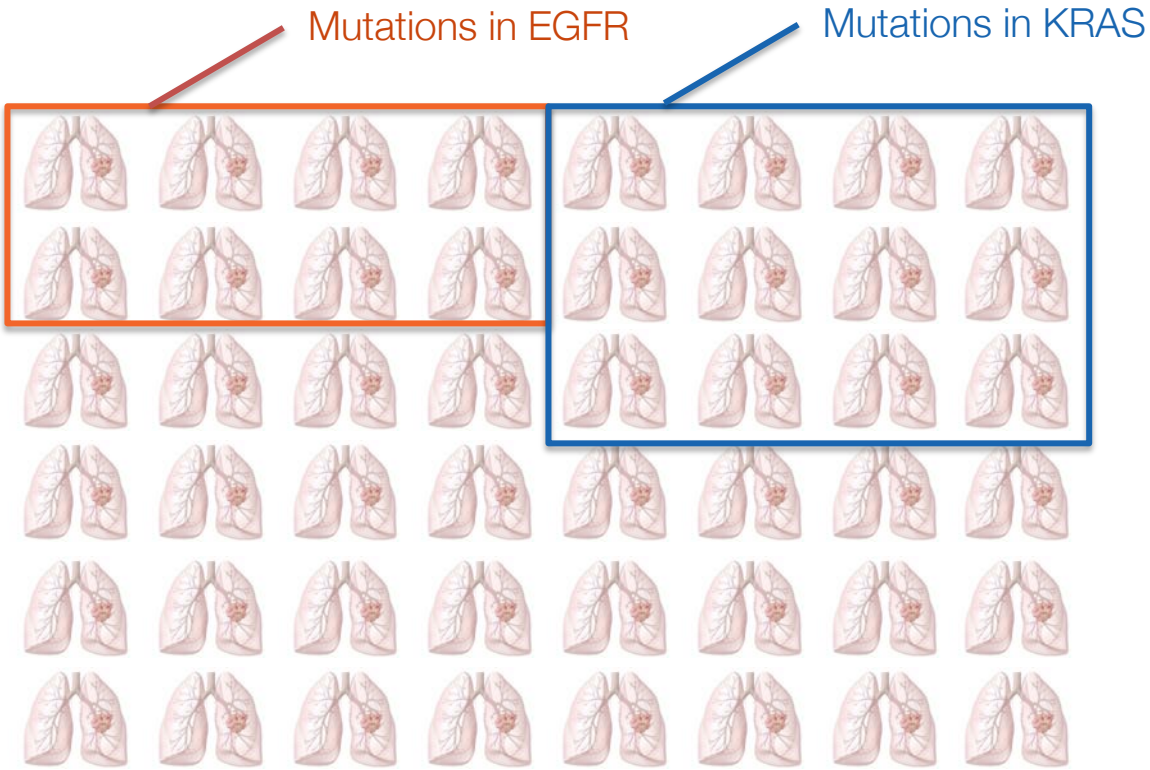


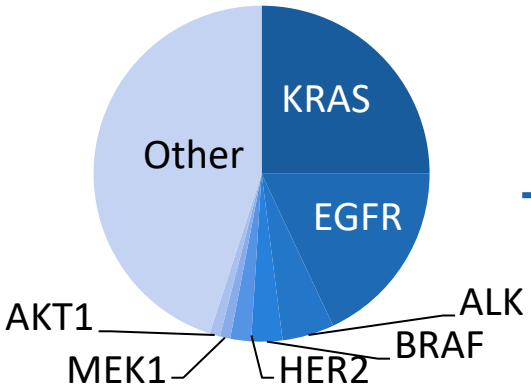


Precision Oncology



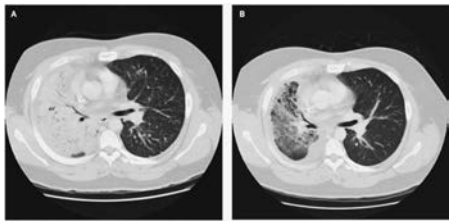
Cancer is a disease of the genome

Lung Cancer



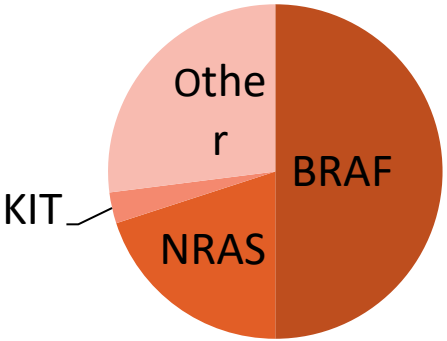
EGFR-mutant cancer

EGFR inhibitors:
erlotinib, gefinitib



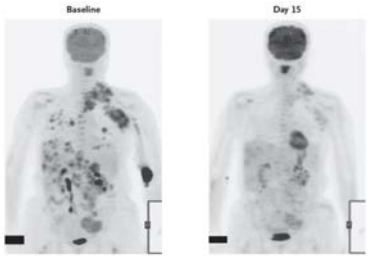
Lynch et al., NEJM, 2004
Paez et al., Science, 2004
Pao et al., PNAS, 2004

Melanoma



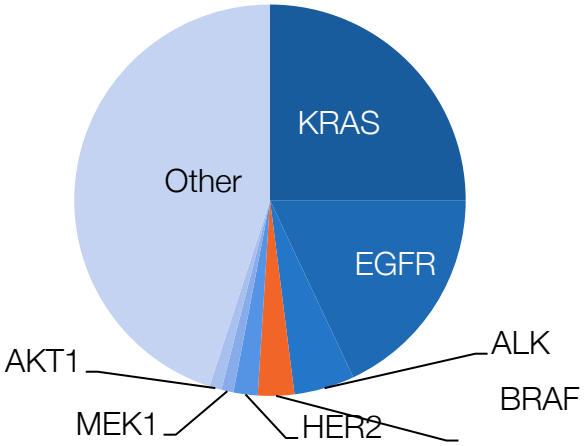
BRAF-mutant cancer

BRAF inhibitor:
vemurafenib, dabrafenib

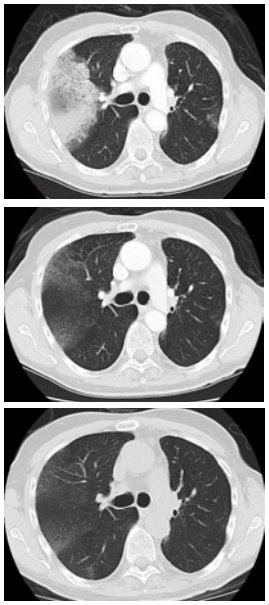


Flaherty et al., NEJM, 2010

Lung Cancer



Response to Dabrafenib



Baseline

6 weeks on Dabrafenib

4 months on Dabrafenib

Courtesy Dr. Greg Riely