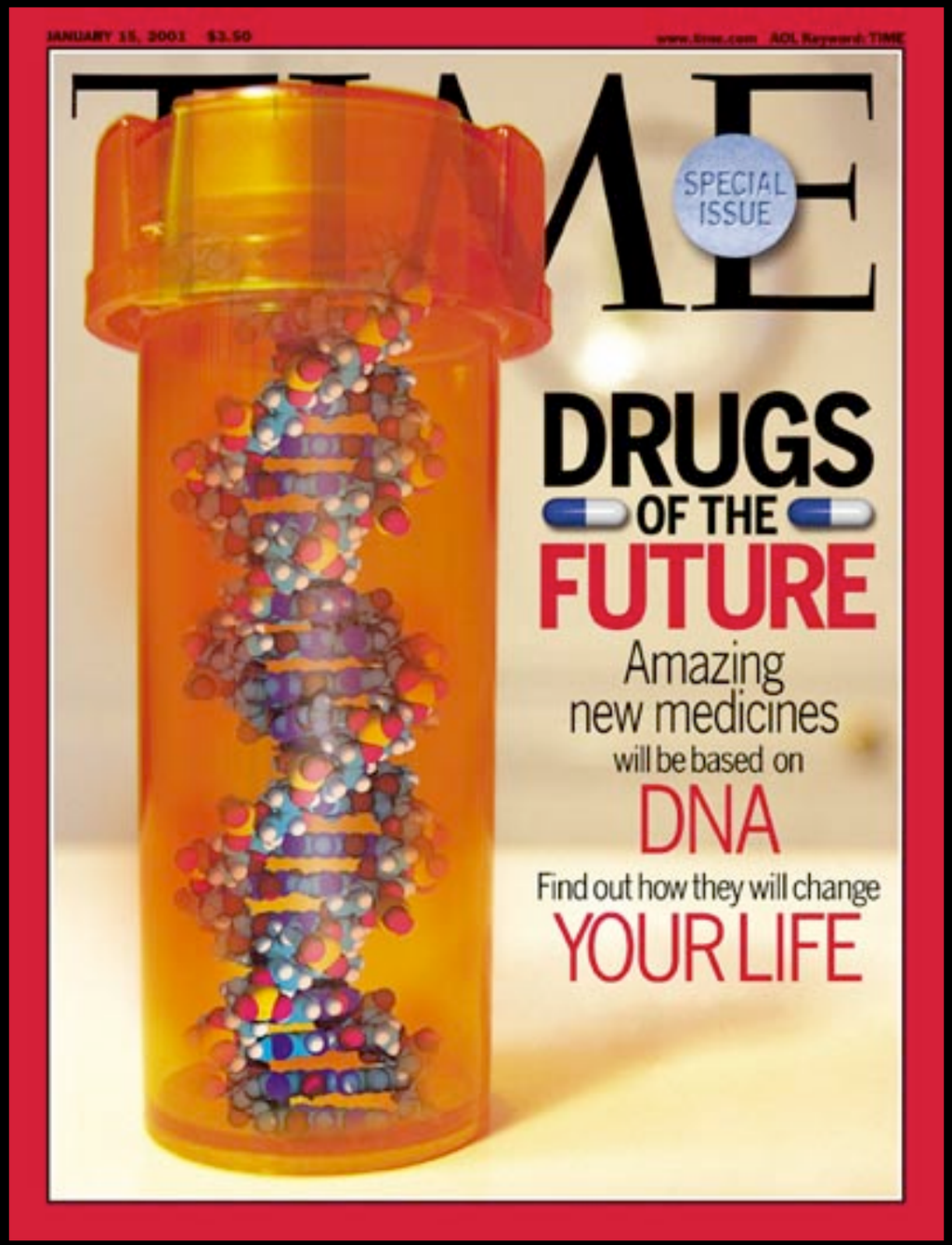
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TIME
SPECIAL ISSUE
DRUGS OF THE FUTURE
Amazing new medicines will be based on
DNA
Find out how they will change
YOUR LIFE

Precision Medicine

"Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

Precision Medicine: Cancer Drugs

Adenocarcinoma of the stomach or gastroesophageal junction: Trastuzumab (Herceptin®), ramucirumab (Cyramza®)

Basal cell carcinoma: Vismodegib (Erivedge™), sonidegib (Odomzo®)

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

Breast cancer: Everolimus (Afinitor®), tamoxifen, toremifene (Fareston®), Trastuzumab (Herceptin®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), lapatinib (Tykerb®), letrozole (Femara®), pertuzumab (Perjeta™), ado-trastuzumab emtansine (Kadcyla™), palbociclib (Ibrance®)

Cervical cancer: Bevacizumab (Avastin®)

Colorectal cancer: Cetuximab (Erbitux®), panitumumab (Vectibix®), bevacizumab (Avastin®), ziv-aflibercept (Zaltrap®), regorafenib (Stivarga®), ramucirumab (Cyramza®)

Dermatofibrosarcoma protuberans: Imatinib mesylate (Gleevec®)

Endocrine/neuroendocrine tumors: Lanreotide acetate (Somatuline® Depot)

Head and neck cancer: Cetuximab (Erbitux®)

Gastrointestinal stromal tumor: Imatinib mesylate (Gleevec®), sunitinib (Sutent®), regorafenib (Stivarga®)

Giant cell tumor of the bone: Denosumab (Xgeva®)

Kaposi sarcoma: Alitretinoin (Panretin®)

Kidney cancer: Bevacizumab (Avastin®), sorafenib (Nexavar®), sunitinib (Sutent®), pazopanib (Votrient®), temsirolimus (Torisel®), everolimus (Afinitor®), axitinib (Inlyta®)

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™)

Liver cancer: Sorafenib (Nexavar®)

Lung cancer: Bevacizumab (Avastin®), crizotinib (Xalkori®), erlotinib (Tarceva®), gefitinib (Iressa®), afatinib dimaleate (Gilotrif®), ceritinib (LDK378/Zykadia), ramucirumab (Cyramza®), nivolumab (Opdivo®)

Lymphoma: Ibritumomab tiuxetan (Zevalin®), denileukin diftitox (Ontak®), brentuximab vedotin (Adcetris®), rituximab (Rituxan®), vorinostat (Zolinza®), romidepsin (Istodax®), bexarotene (Targretin®), bortezomib (Velcade®), pralatrexate (Folotyn®), lenaliomide (Revlimid®), ibrutinib (Imbruvica™), siltuximab (Sylvant™), idelalisib (Zydelig®), belinostat (Beleodaq™)

Melanoma: Ipilimumab (Yervoy®), vemurafenib (Zelboraf®), trametinib (Mekinist®), dabrafenib (Tafinlar®), pembrolizumab (Keytruda®), nivolumab (Opdivo®)

Multiple myeloma: Bortezomib (Velcade®), carfilzomib (Kyprolis®), lenaliomide (Revlimid®), pomalidomide (Pomalyst®), panobinostat (Farydak®)

Myelodysplastic/myeloproliferative disorders: Imatinib mesylate (Gleevec®), ruxolitinib phosphate (Jakafi™)

Neuroblastoma: Dinutuximab (Unituxin™)

Ovarian epithelial/fallopian tube/primary peritoneal cancers: Bevacizumab (Avastin®), olaparib (Lynparza™)

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

Prostate cancer: Cabazitaxel (Jevtana®), enzalutamide (Xtandi®), abiraterone acetate (Zytiga®), radium 223 chloride (Xofigo®)

Soft tissue sarcoma: Pazopanib (Votrient®)

Systemic mastocytosis: Imatinib mesylate (Gleevec®)

Thyroid cancer: Cabozantinib (Cometriq™), vandetanib (Caprelsa®), sorafenib (Nexavar®), lenvatinib mesylate (Lenvima™)

Precision drugs: magic bullets against cancer?

Published online 7 September 2010 | *Nature* **467**, 140-141 (2010) | doi:10.1038/467140b

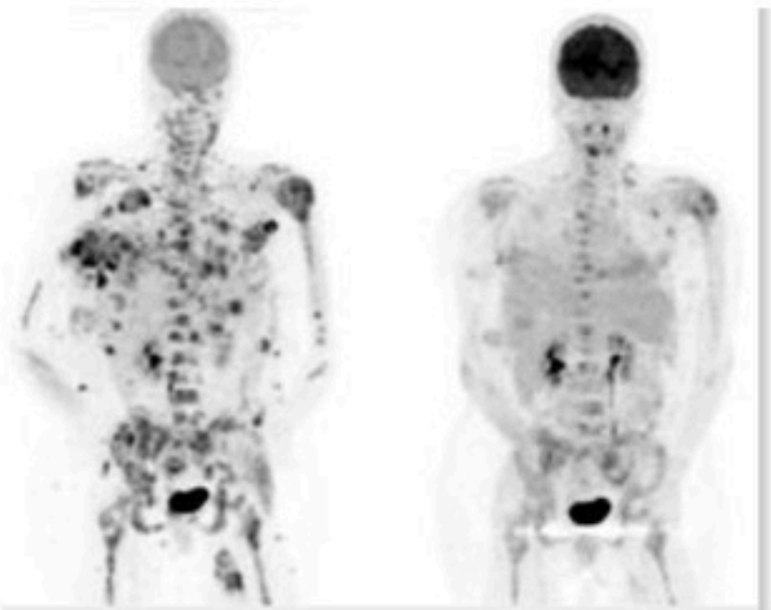
News

Rare victory in fight against melanoma

Genetically tailored approach could slow disease progress.

Heidi Ledford

Patients with advanced melanoma rarely live for more than a year after their diagnosis — a prognosis that has not improved for more than 30 years. But clinical-trial results[1] now suggest that a genetically targeted approach could slow the disease's steady march through the body, and separate research[2] reveals why the latest drug being tested may succeed where others failed.



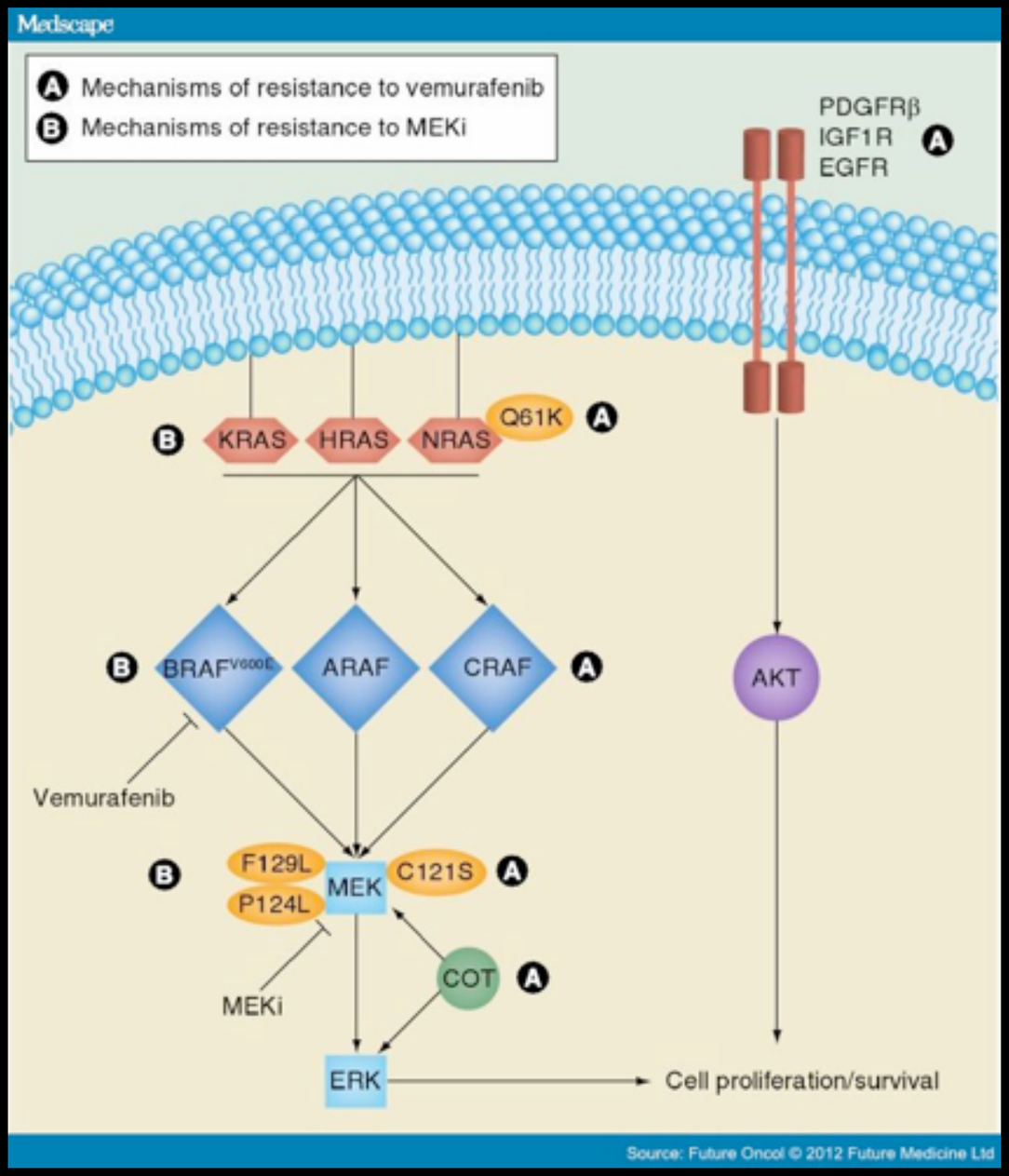
Melanoma tumours shrank after patients took PLX4032 for 2 weeks.

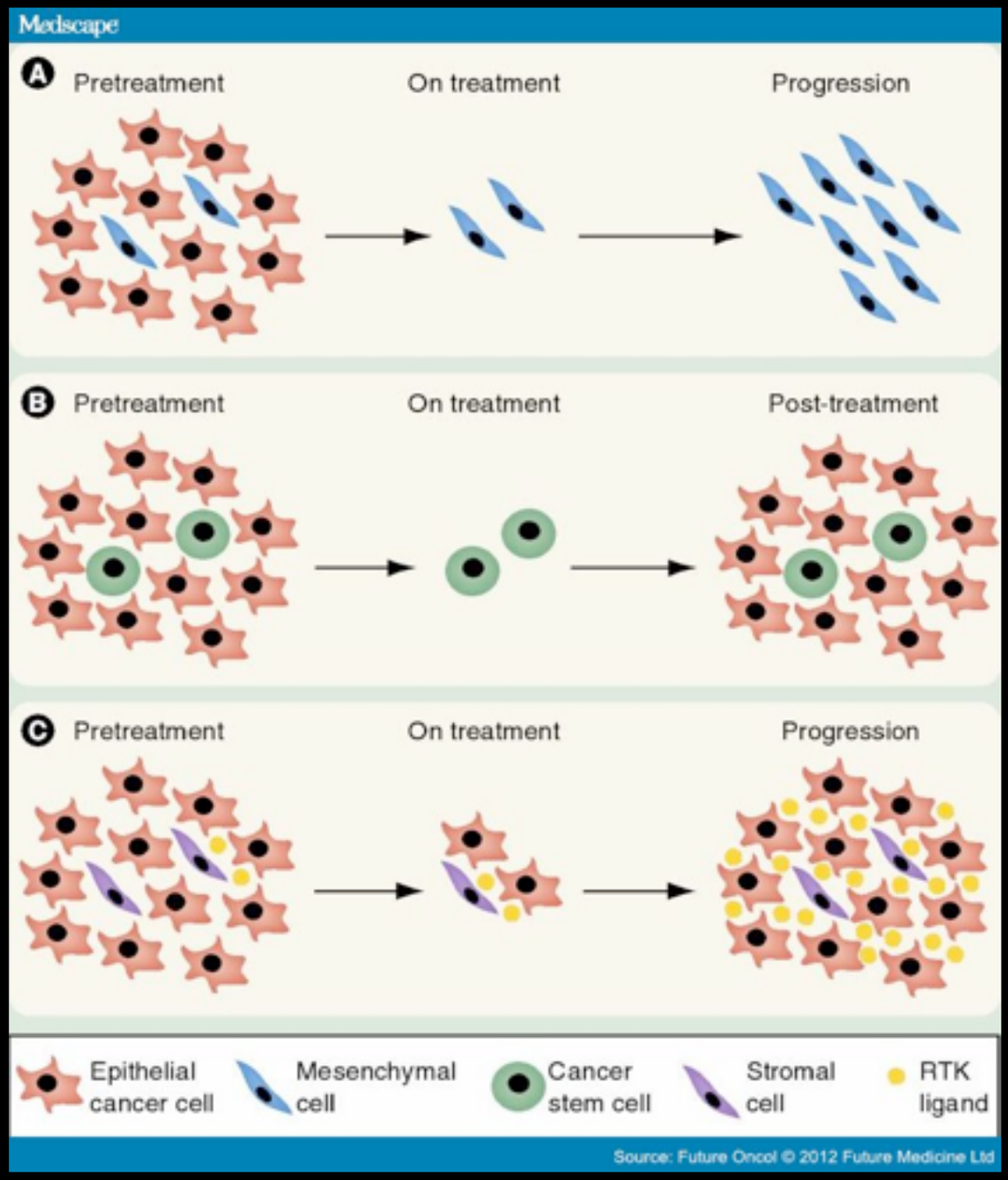
REF. 2

A common pitfall of targeted therapies: Acquired Resistance

A common pitfall of targeted therapies: Acquired Resistance

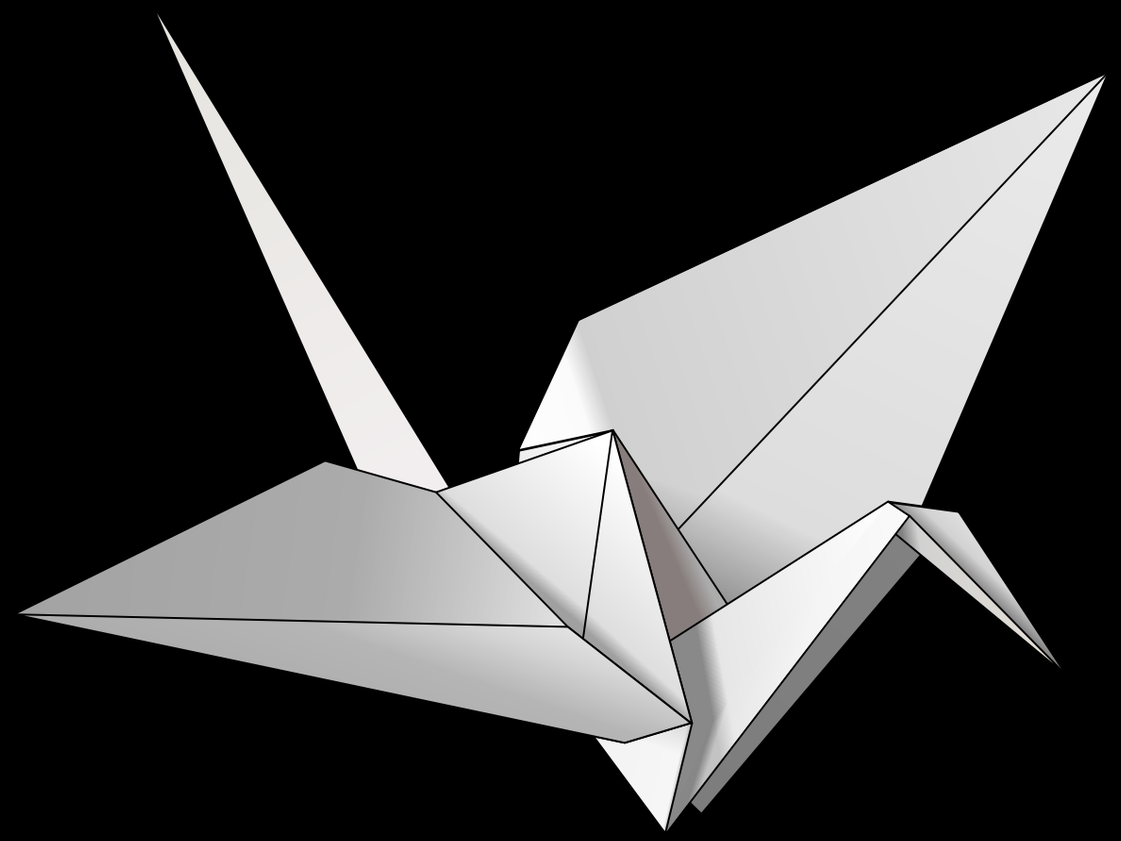
Genetic and Non-genetic routes to acquired resistance





Targeted drugs + Precision control

Precision Control of Protein Folding to treat Cancer and Neurodegeneration



David Pincus
pincus@wi.mit.edu
Whitehead Institute for Biomedical Research

commons.wikimedia.org

By the year 2050...

Cancer (all types)

- 17.5 million deaths/year
- $1.7 trillion/year

American Cancer Society

By the year 2050...

Alzheimer's

- 115.4 million dementia cases
- $1.1 trillion/year

World Health Organization

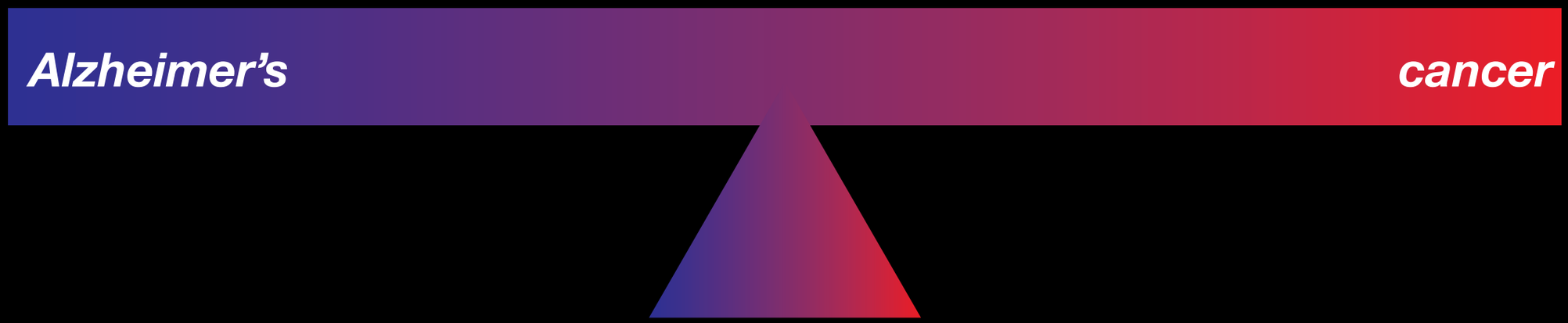
Cancer and Alzheimer's are on opposite ends of the disease spectrum

Alzheimer's — ***cancer***

premature cell death

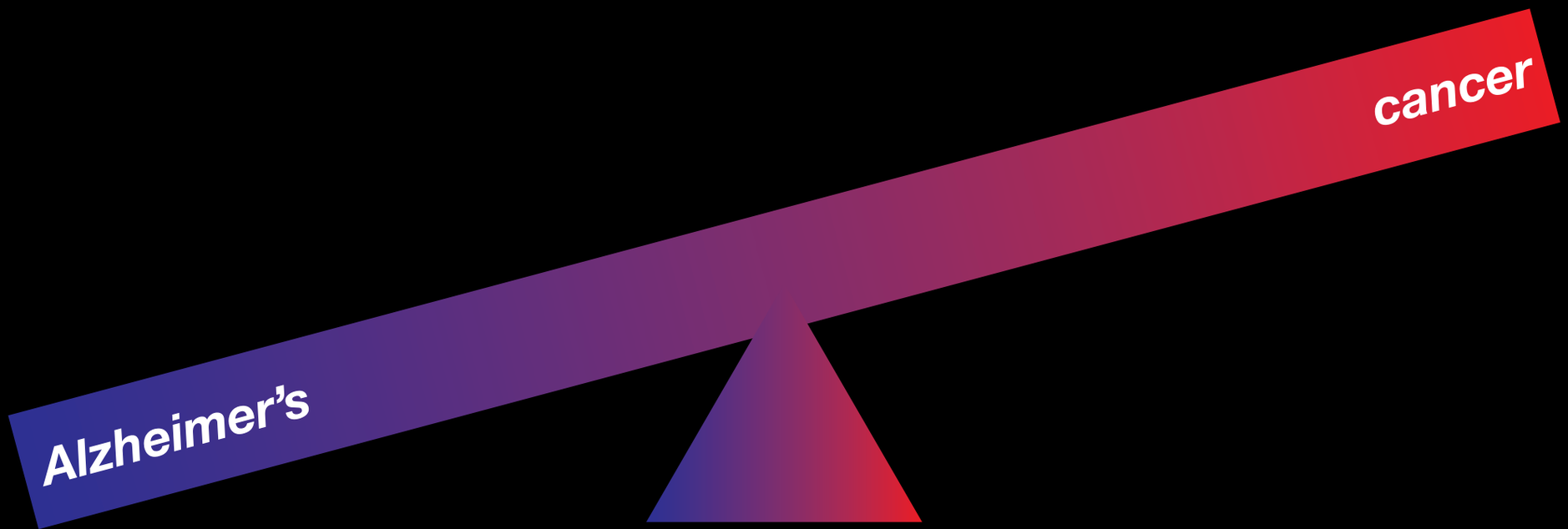
unchecked cell growth

Patients with Alzheimer's have a lower incidence of cancer and vice versa



e.g., Musicco et al. 2013, *Neurology*

Patients with Alzheimer's have a lower incidence of cancer and vice versa



e.g., Musicco et al. 2013, *Neurology*

Patients with Alzheimer's have a lower incidence of cancer and vice versa

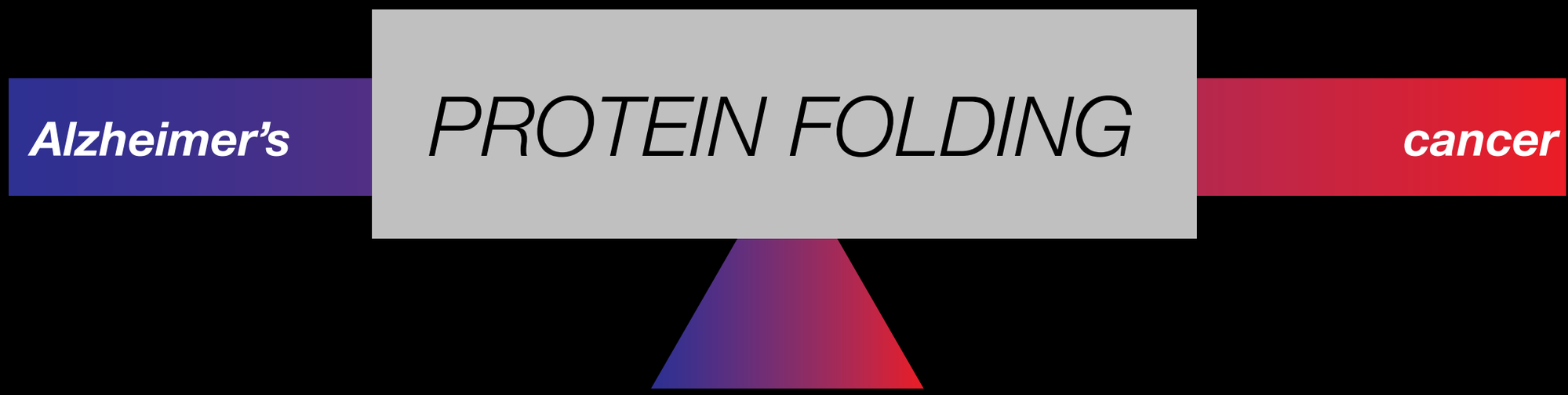
e.g., Musicco et al. 2013, *Neurology*

Patients with Alzheimer's have a lower incidence of cancer and vice versa

Same is true for Parkinson's and ALS vs. cancer

e.g., Musicco et al. 2013, *Neurology*

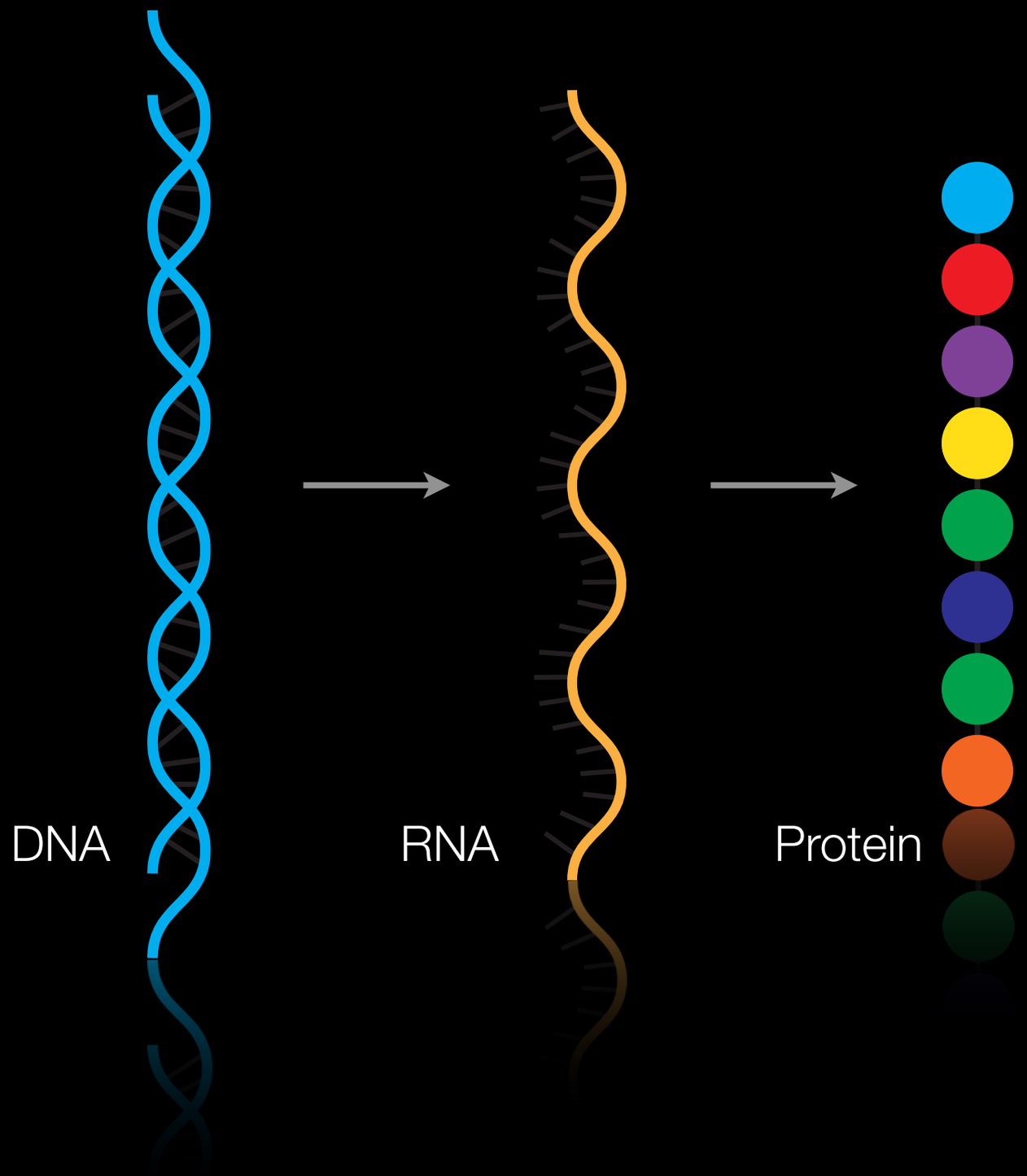
Patients with Alzheimer's have a lower incidence of cancer and vice versa



Same is true for Parkinson's and ALS vs. cancer

e.g., Musicco et al. 2013, *Neurology*

Genes (DNA) encode instructions to make strings of amino acids called proteins



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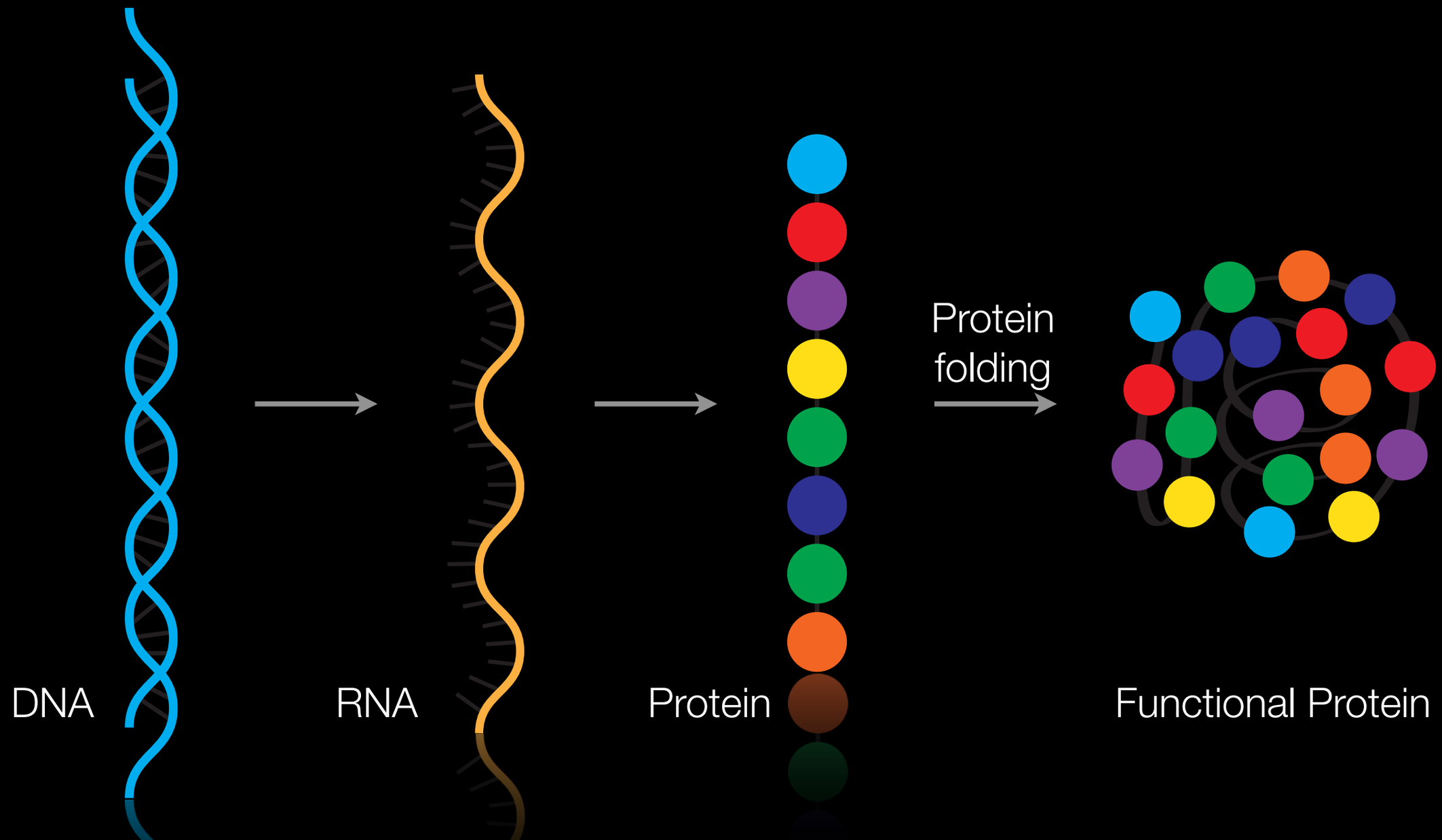
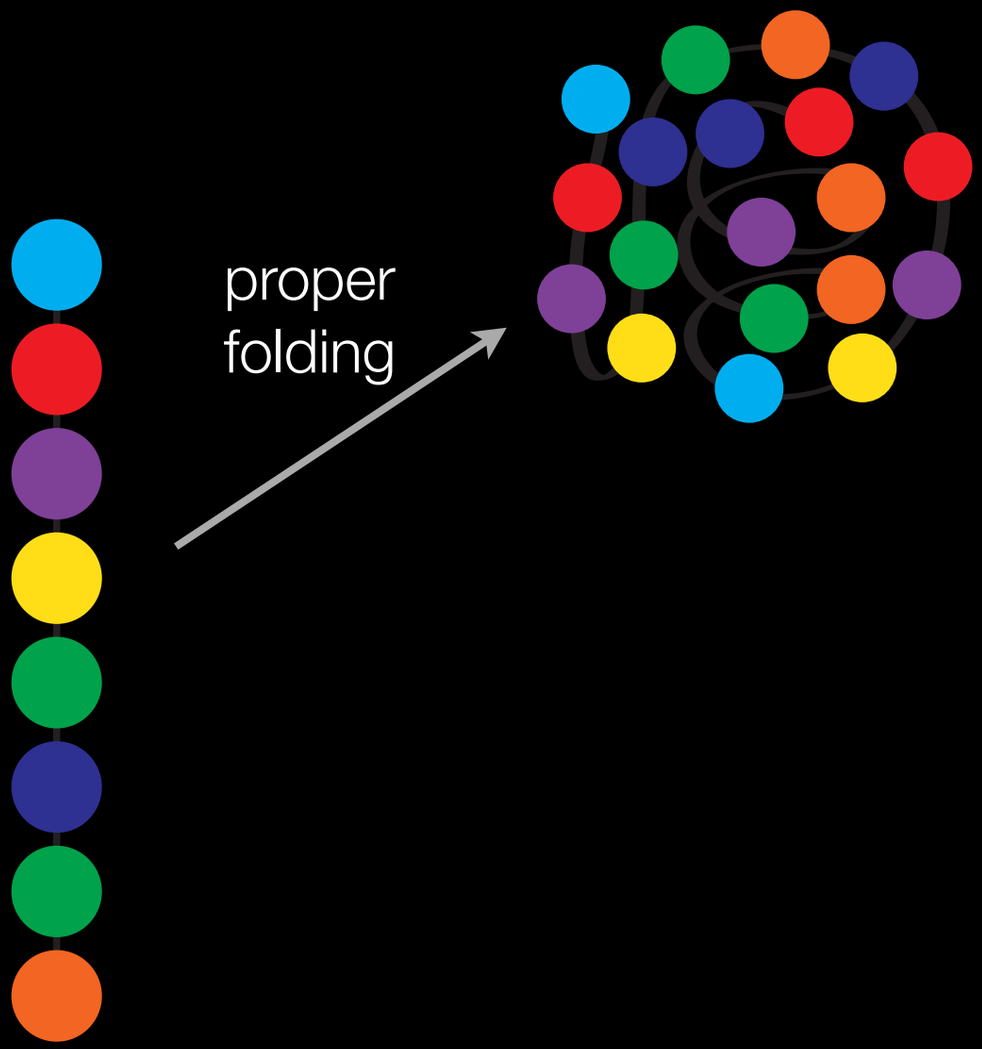
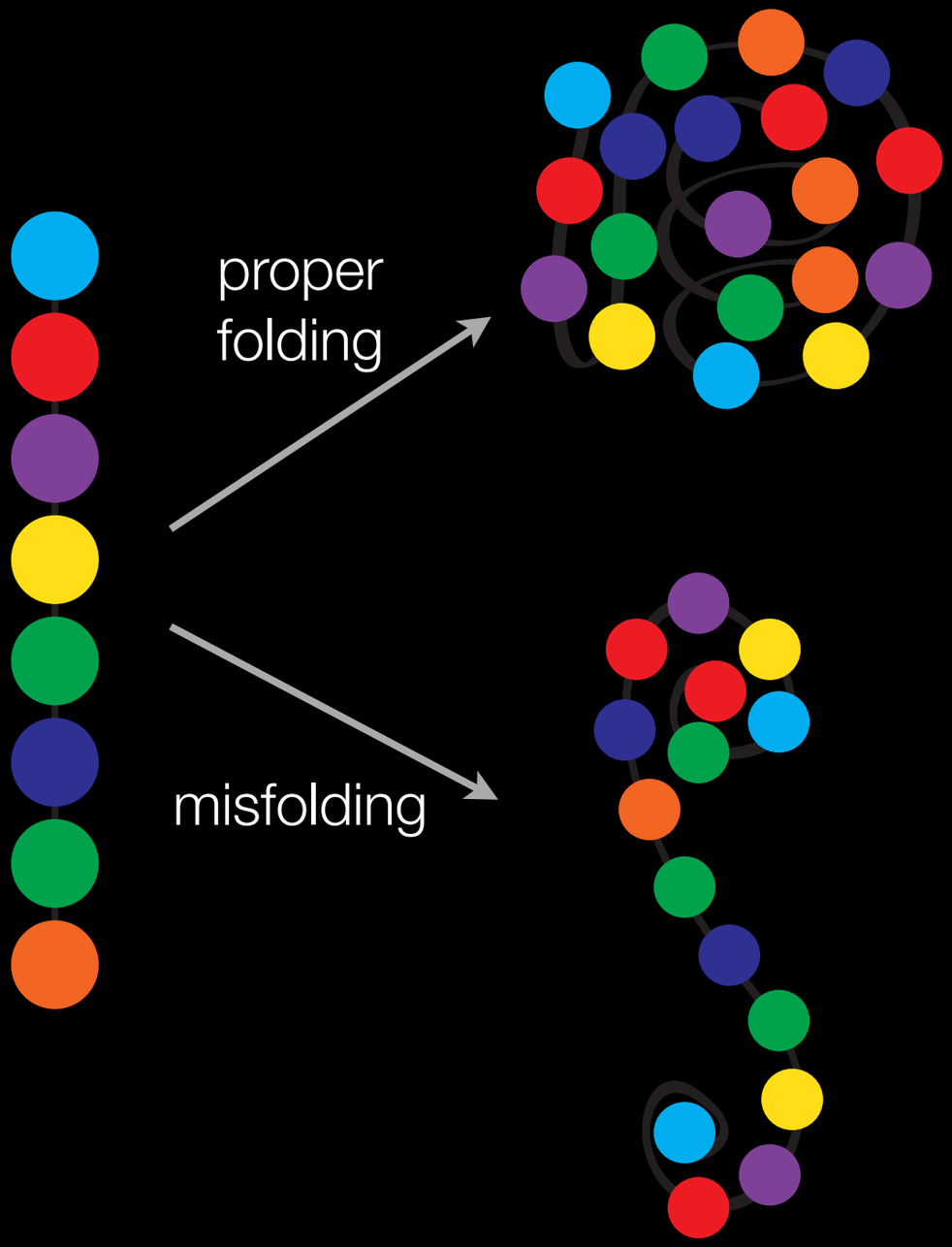


Proteins must “fold” correctly to carry out their functions

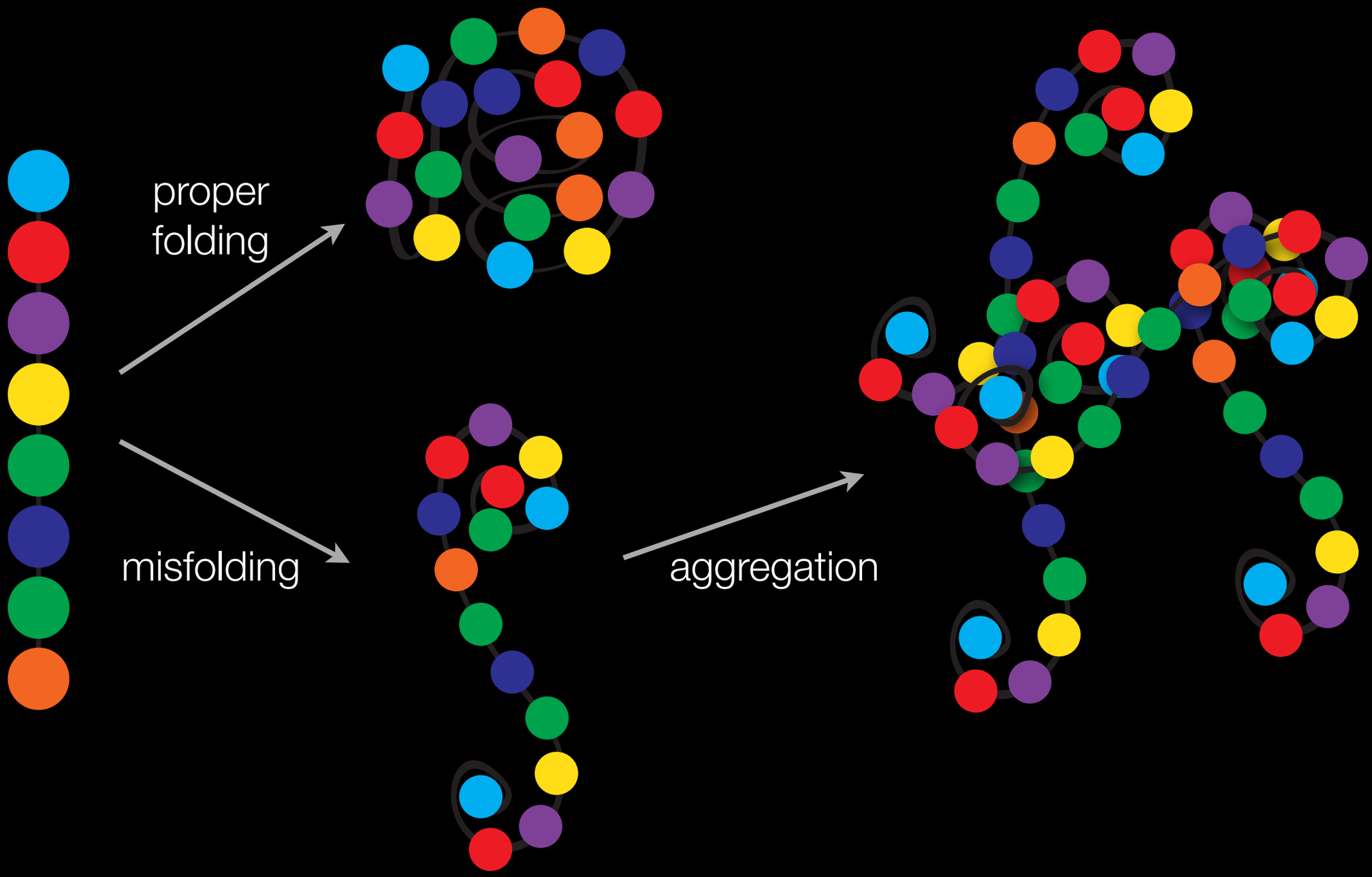
Proteins do not always fold properly



Proteins do not always fold properly

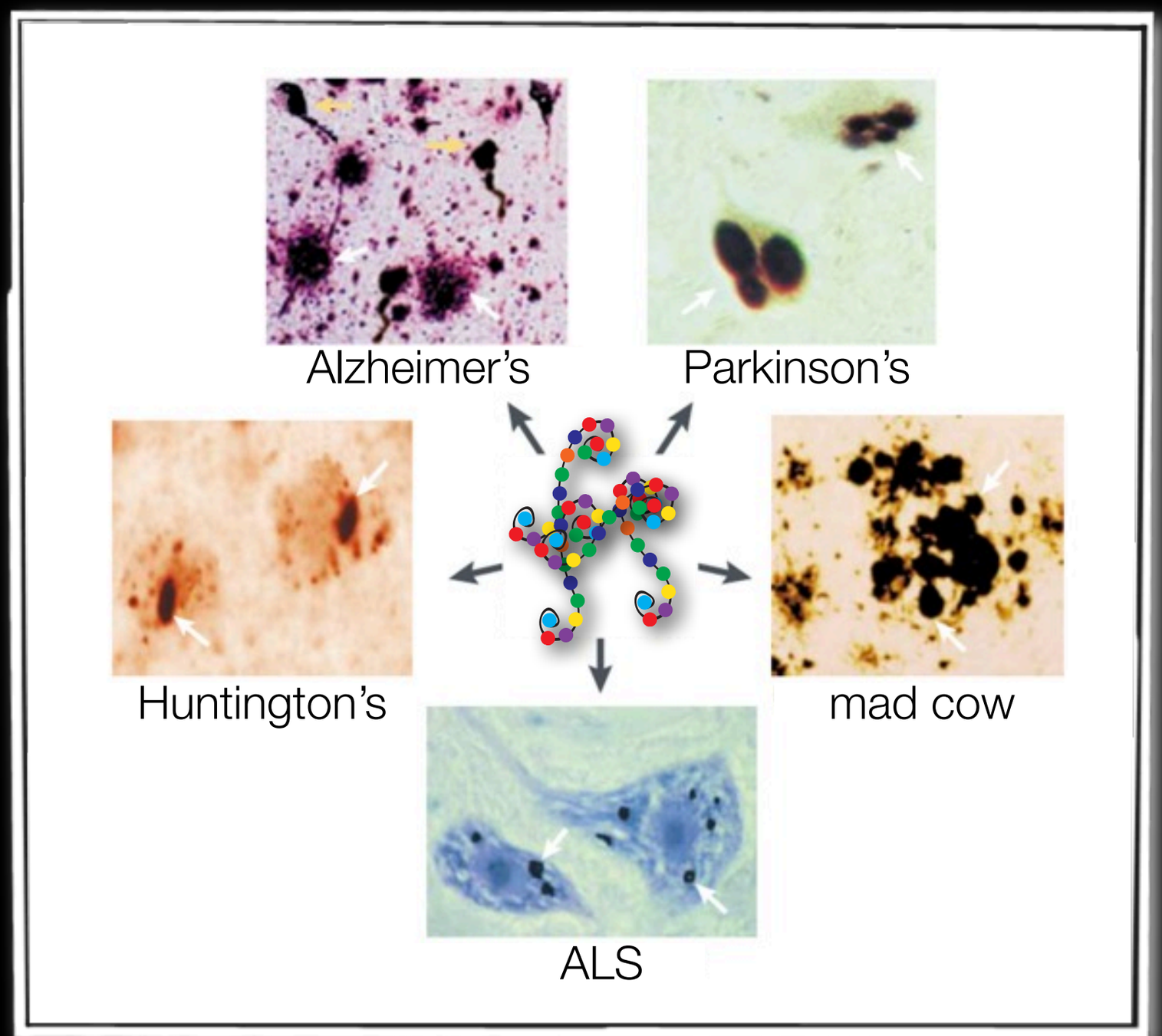


Proteins do not always fold properly



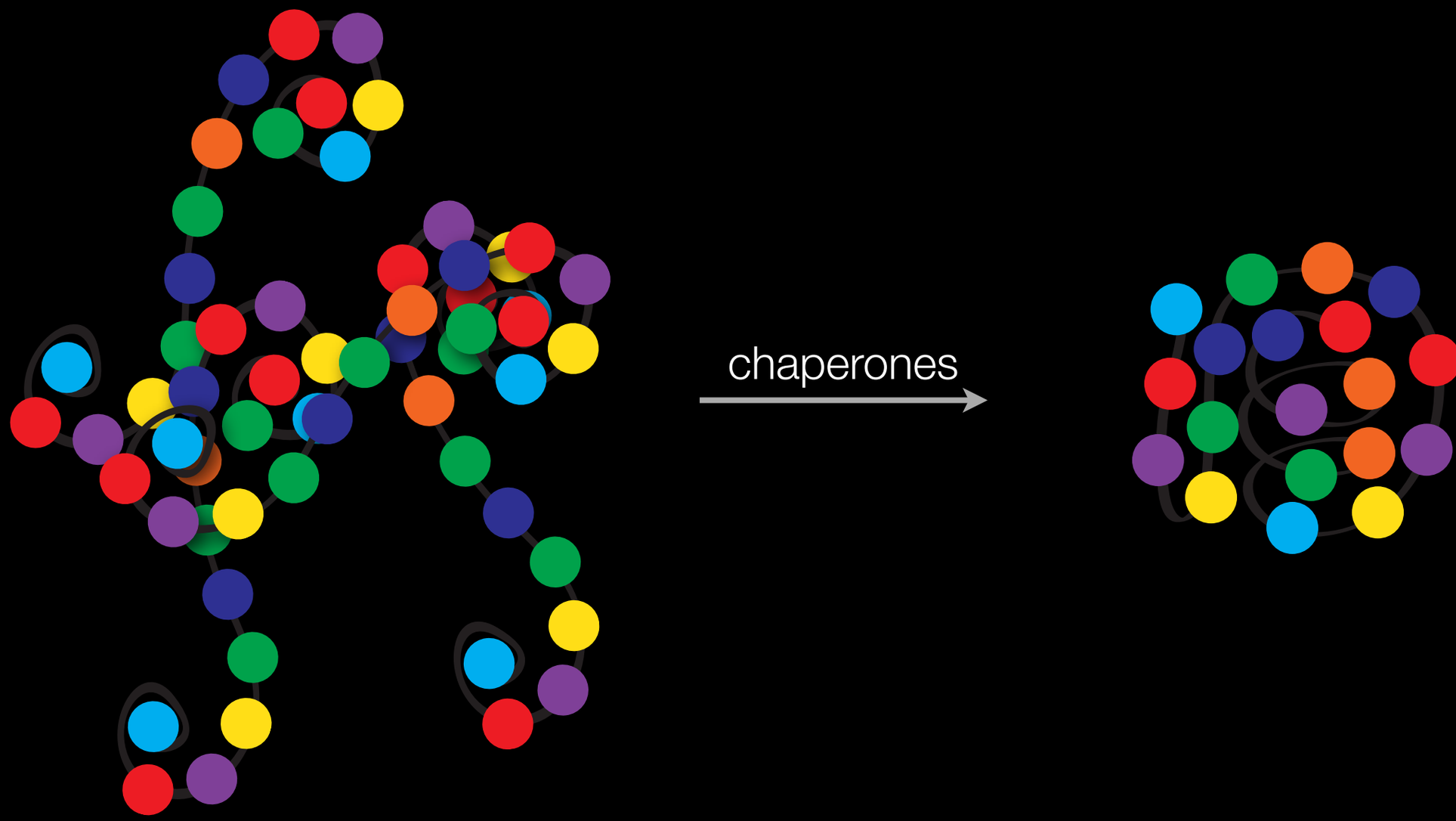
misfolded proteins form aggregates

Protein aggregates are a hallmark of diseases like Alzheimer's



modified from Soto 2003, *Nat. Rev. Neuroscience*

Chaperones help proteins fold to prevent aggregation



Just like chaperones at your high school dance...

images modified from:
daily-player.com
Meredith Brandimore
netra.sptimes.com/tb-two

Just like chaperones at your high school dance...

“aggregates”

“folded proteins”

Chaperones prevent proteins from engaging in improper interactions

images modified from:
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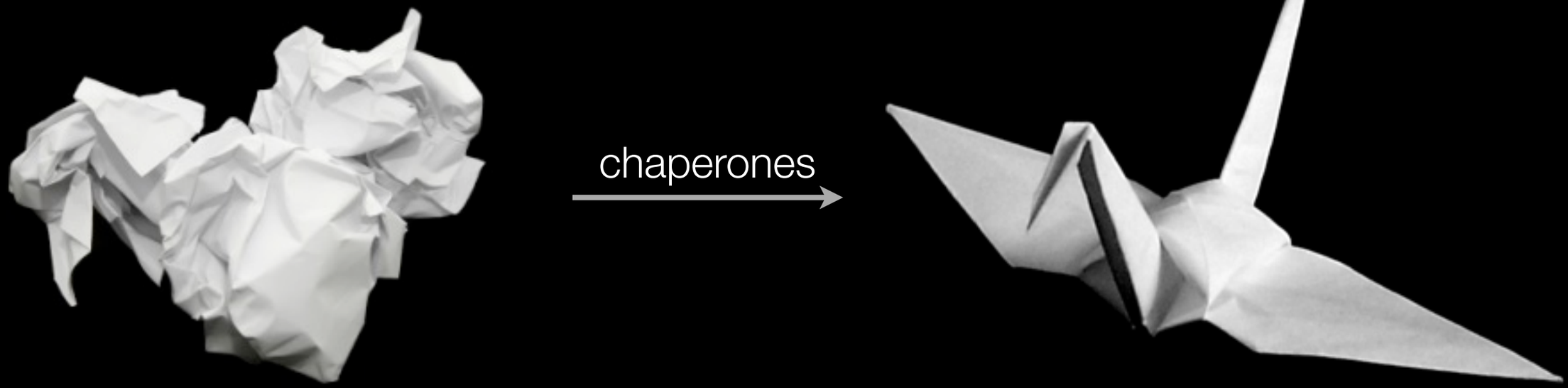
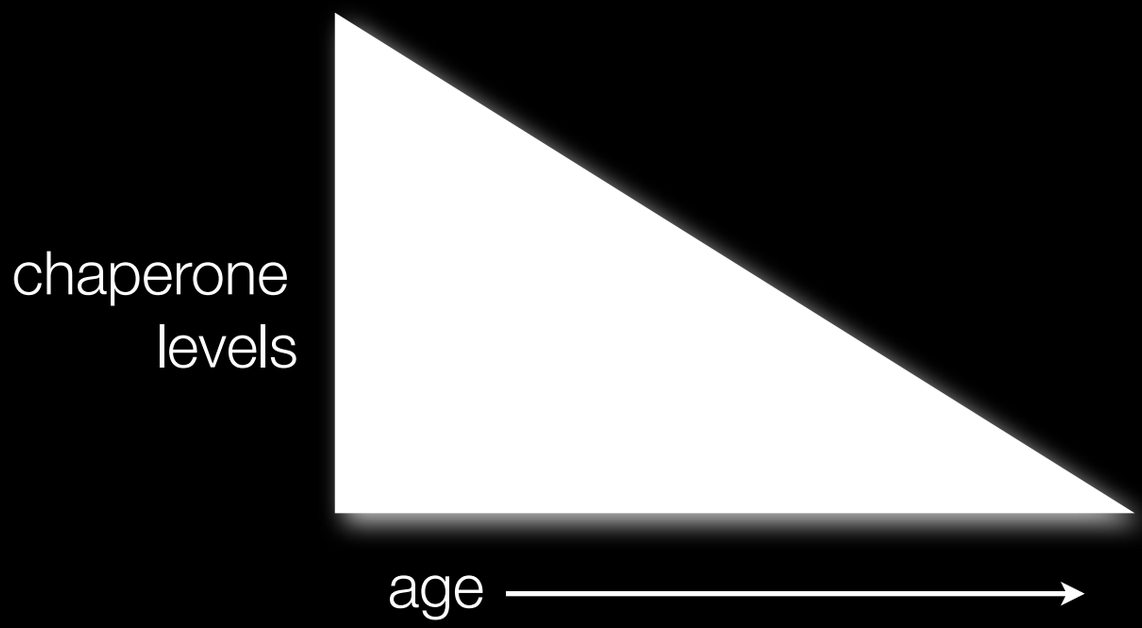
Meredith Brandimore
netra.sptimes.com/tb-two

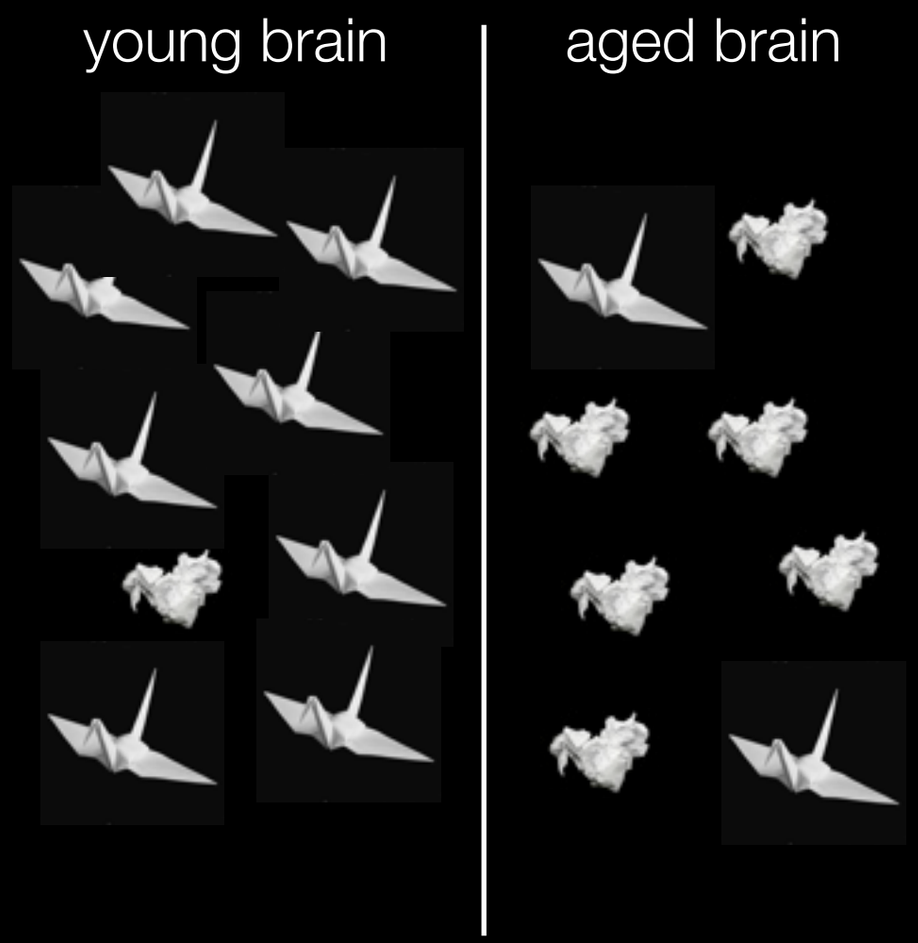
Chaperones perform protein origami



images modified from:
plus.maths.org
simpleorigami.org

Chaperone levels drop in the brain as we age





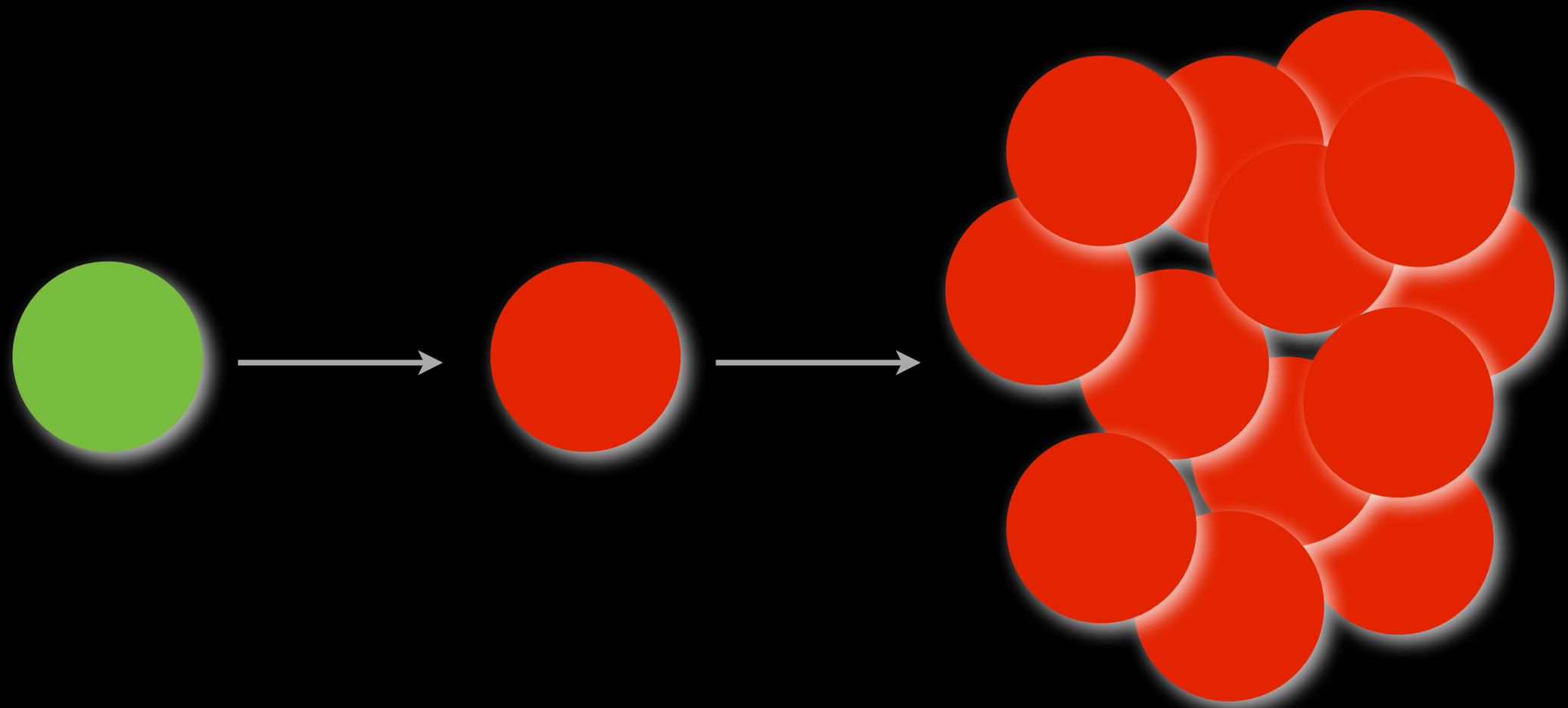
e.g., Yang et al. 2013, *Neuron*

Diseases like Alzheimer's occur in brains with low levels of chaperones.

Diseases like Alzheimer's occur in brains with low levels of chaperones.

If we can ***<u>increase</u>*** chaperones in the brain, we can prevent and reverse these diseases.

Cancer progresses when cells acquire mutations in specific genes

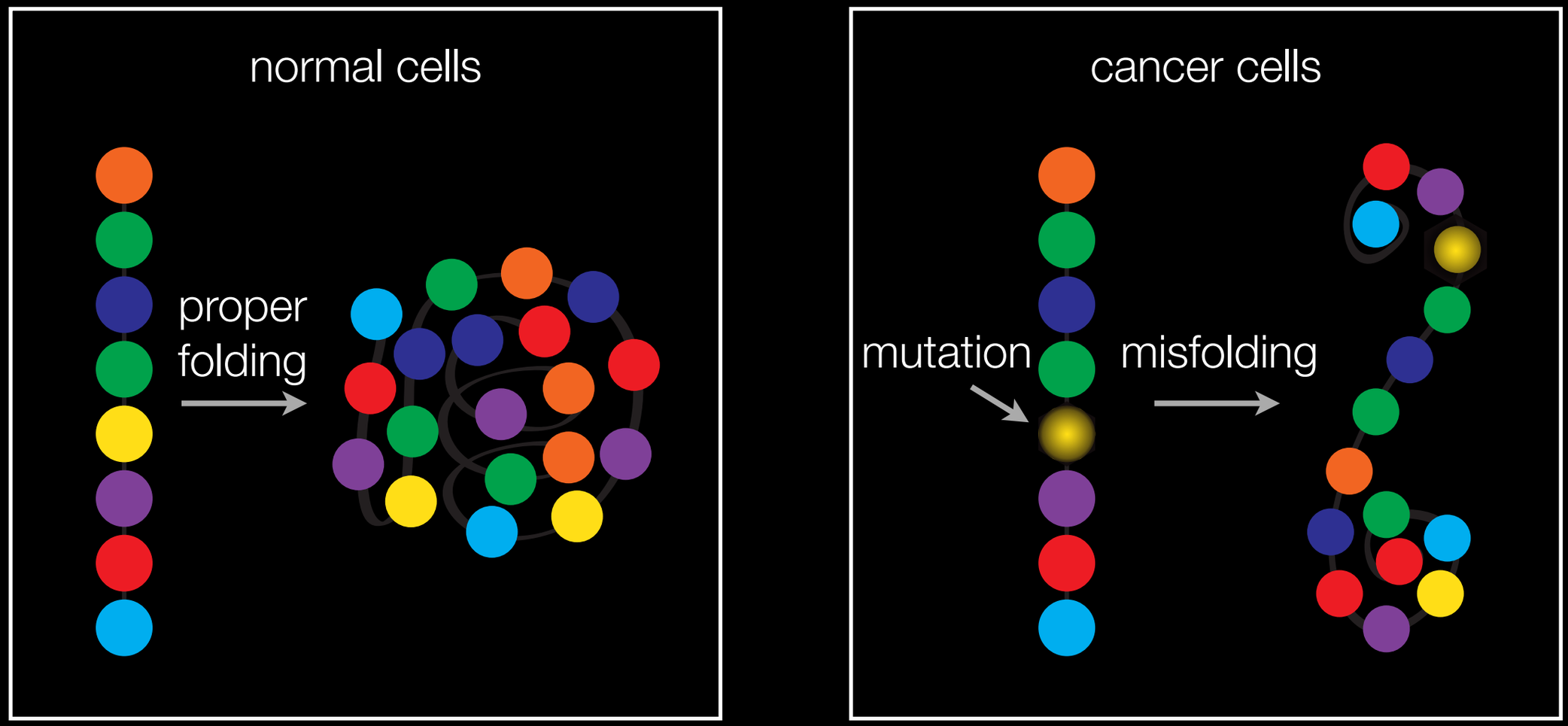


normal cell

mutation arises

unchecked cell growth

Mutations in genes make mutations in proteins



Mutations make proteins difficult to fold

Cancer cells hijack chaperones to counter the effect of mutations

Cancer cells rely on elevated chaperone levels

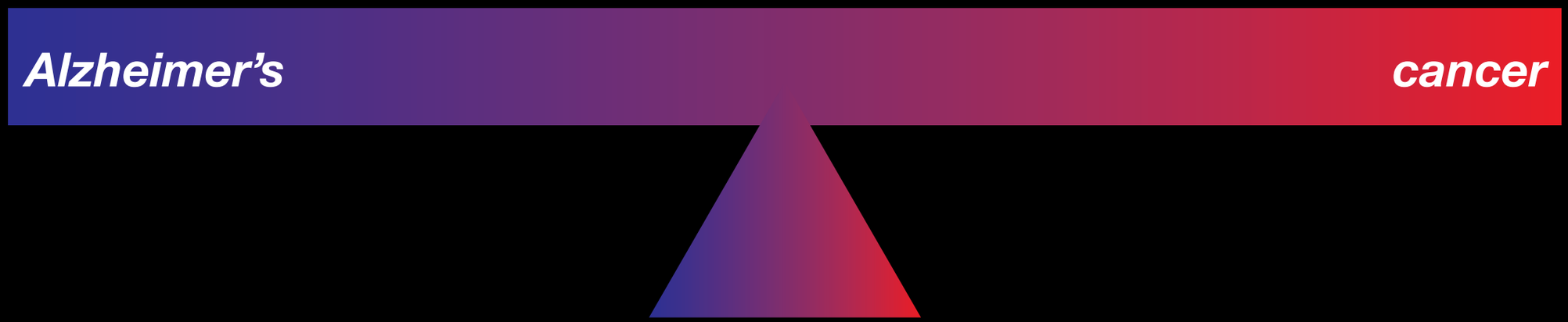
image modified from:
colouringbook.org

Cancer cells hijack chaperones to buffer their mutations.

Cancer cells hijack chaperones to buffer their mutations.

If we can ***decrease*** chaperones in tumors, cancer cells will self-destruct.

Cancer and diseases like Alzheimer's are mutually exclusive due to opposing requirements for chaperones



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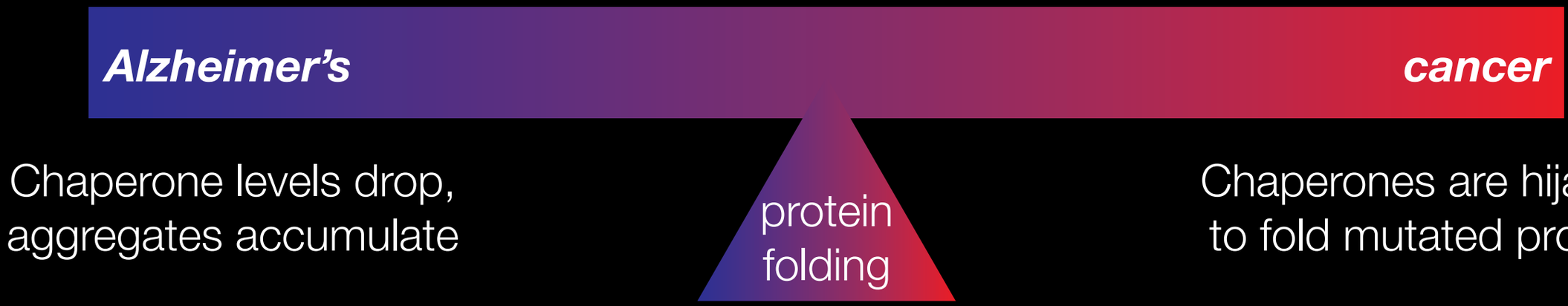


Chaperone levels drop, aggregates accumulate

Chaperones are hijacked to fold mutated proteins

Targeting chaperones is a game of Whack-A-Mole

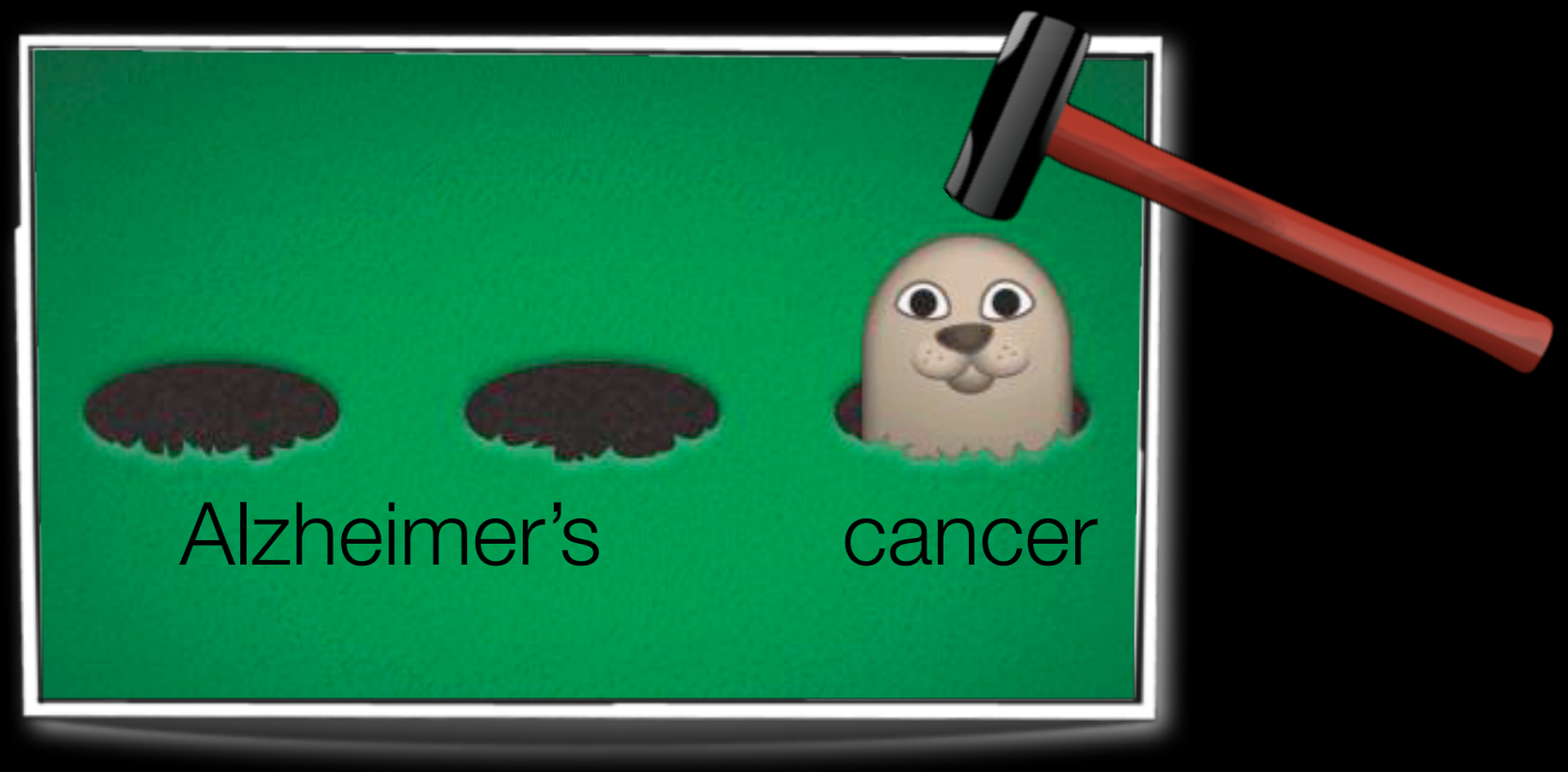
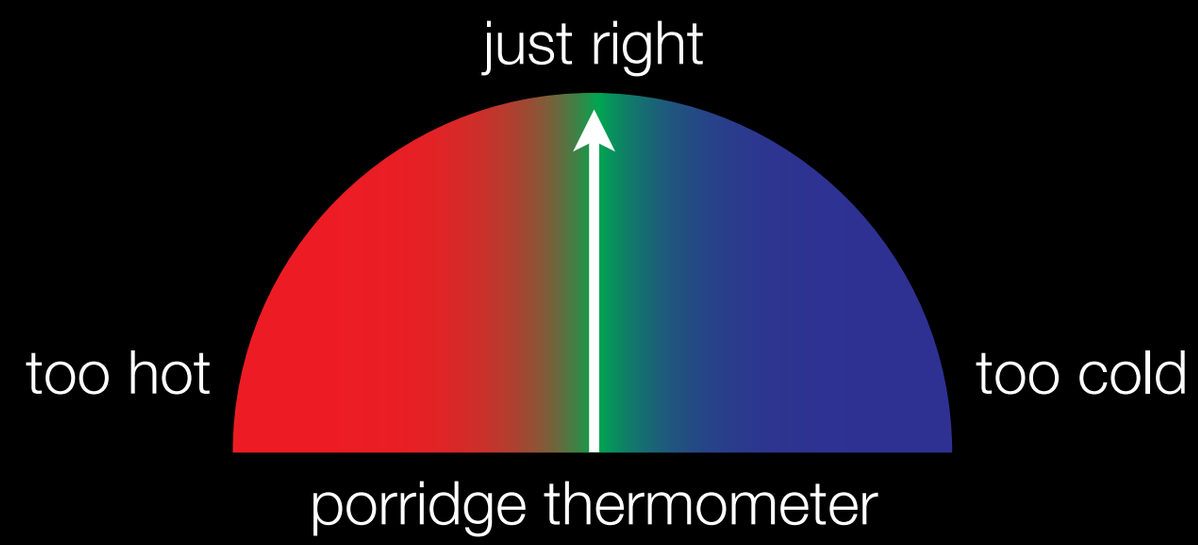


image modified from:
raywenderlich.com

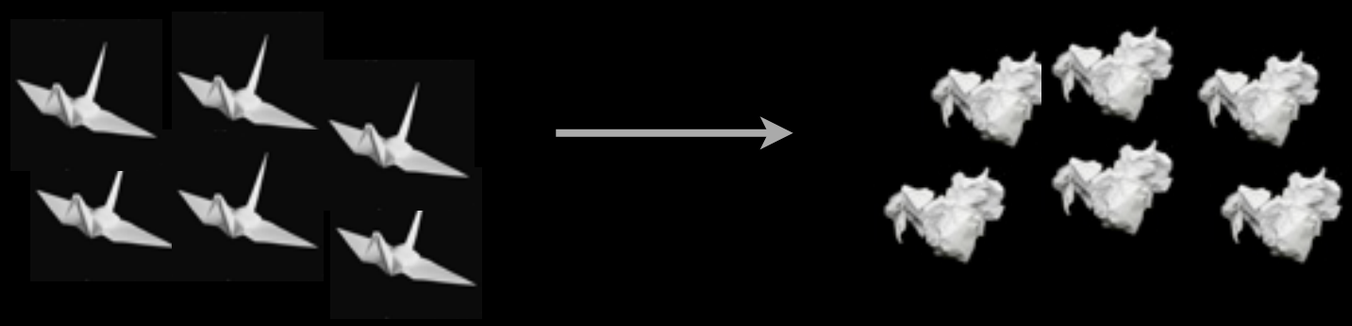
We need a Goldilocks approach



Targeted fine-tuning of chaperone levels is the goal

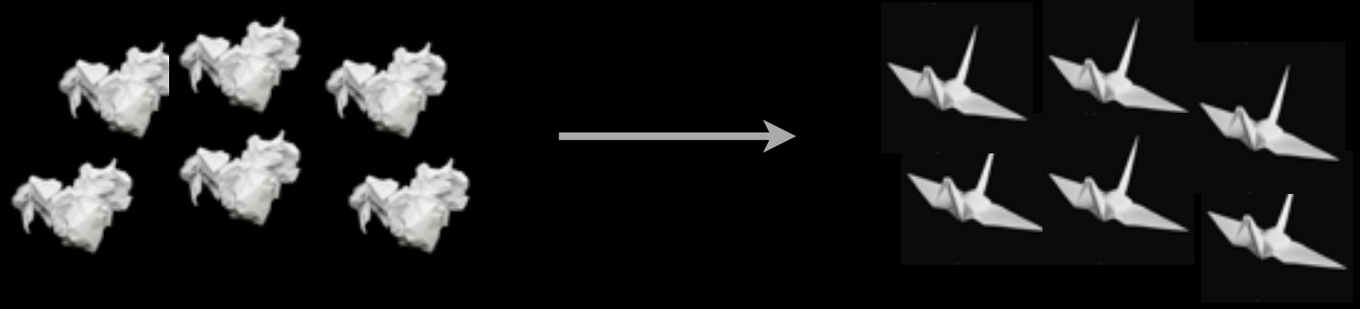
Reducing chaperone levels in a targeted manner is a general approach to treat ***all*** cancer types

(breast, colon, pancreatic, lung, stomach, ovarian ...)

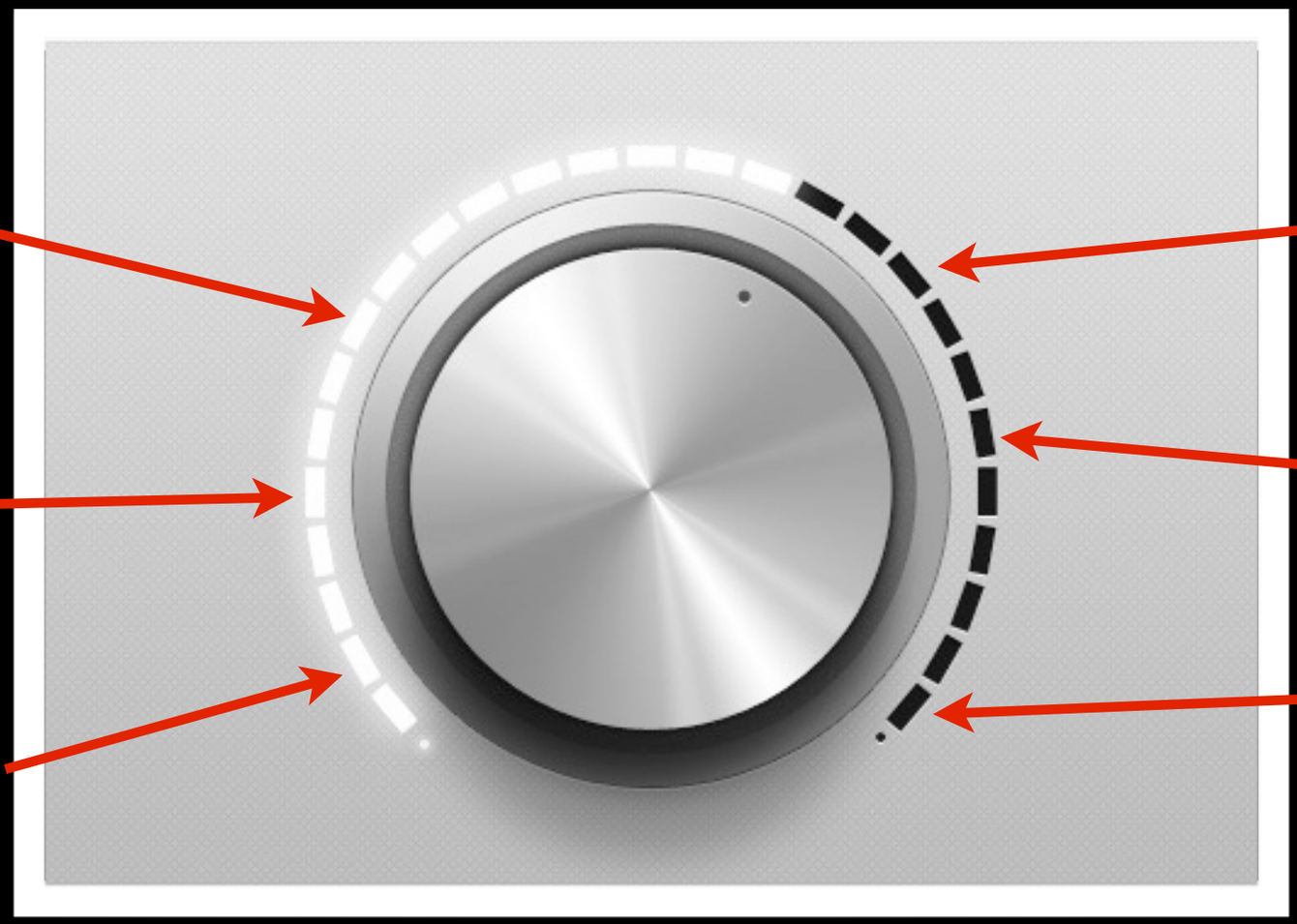


Increasing chaperone levels in the brain
is a general approach to treat ***all***
neurodegenerative diseases

(Alzheimer's, Parkinson's, Huntington's, ALS, FTD ...)

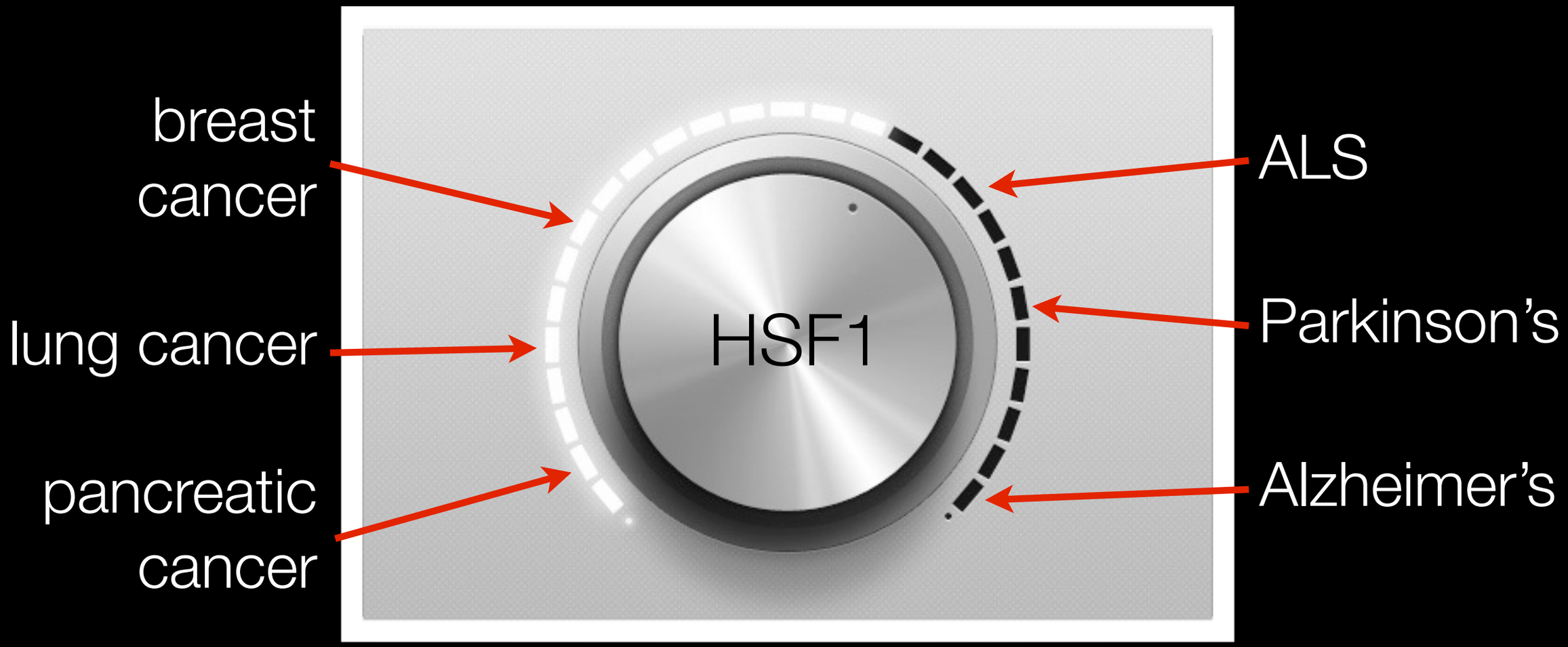


Tuning the chaperone dial for disease-specific therapy



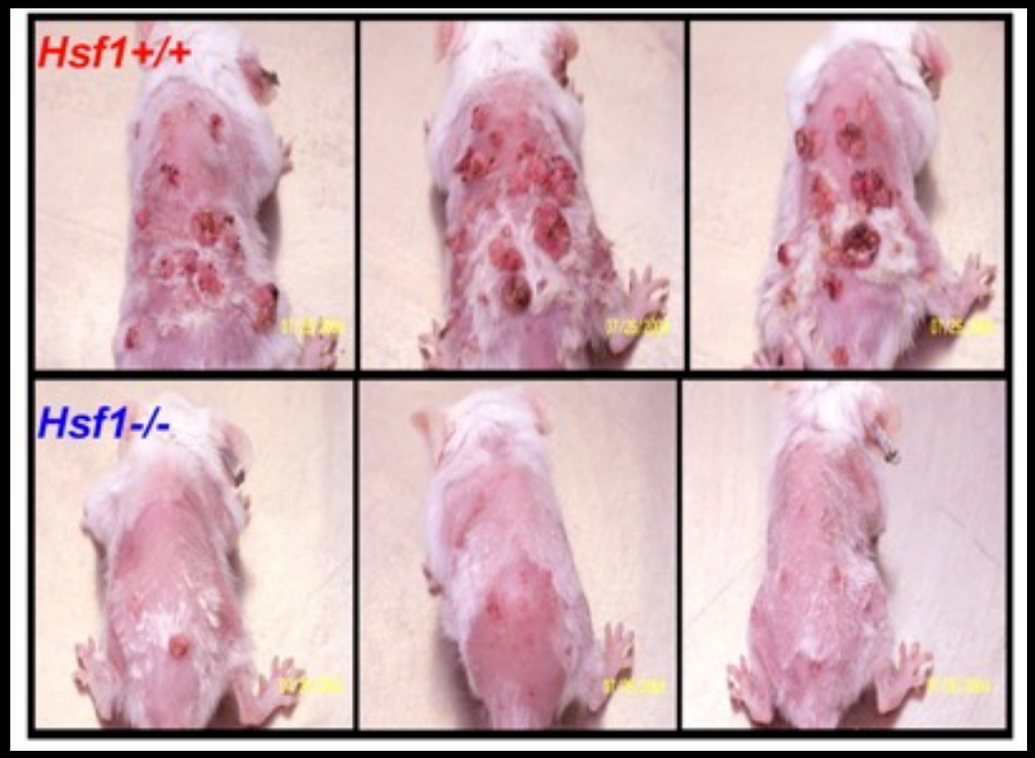
Royce volume knob: uiparade.com

Tuning the chaperone dial for disease-specific therapy



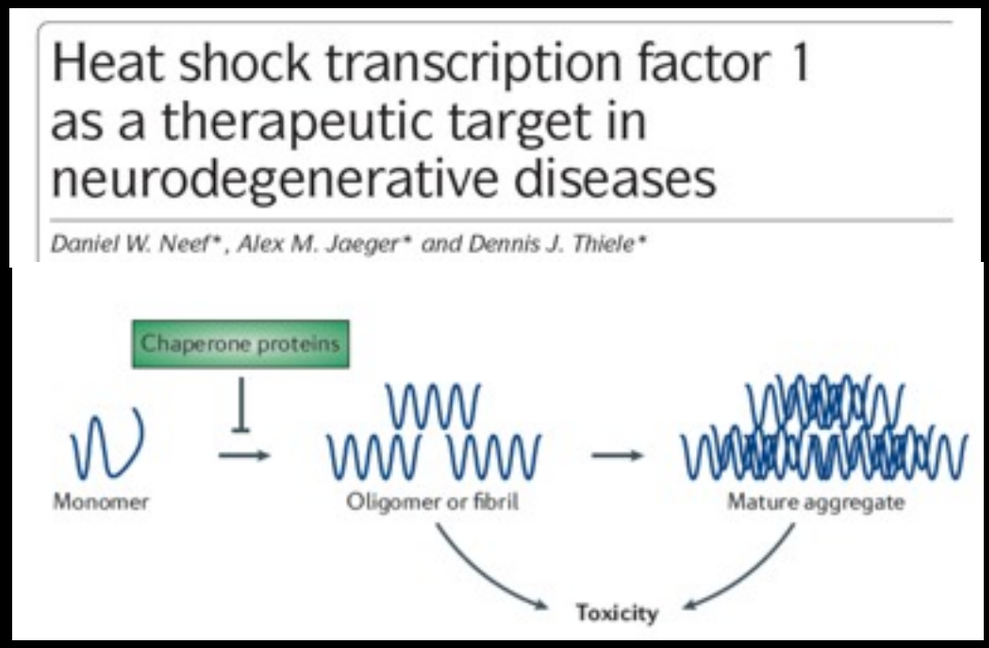
Royce volume knob: uiparade.com

HSF1 is the precision chaperone dial



Dai. et al., 2007

HSF1 is required for cancer progression:
turn it down in cancer



HSF1 stops working in ND diseases:
turn it up in Alzheimer's, etc.

Precision medicine needs a two-pronged approach

1. Target specific mutations that drive diseases (like oncogenes)

2. Fine-tune general cellular support systems (like chaperones)