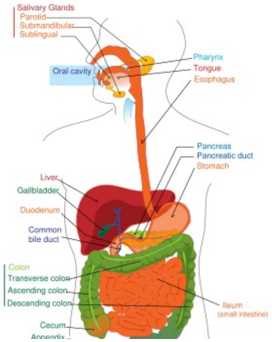
Physical Pharmacology

Chem.physics, math, molecular structure to understand the following:

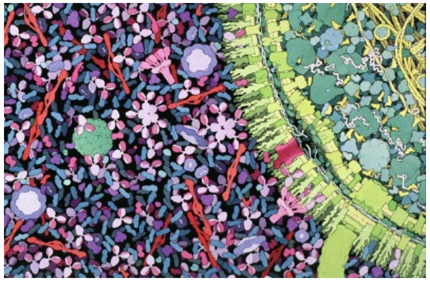
Drug and Drug-action-related Matter

- **Drug substances , bio-molecules, phases, solutions, membranes, and body compartments**



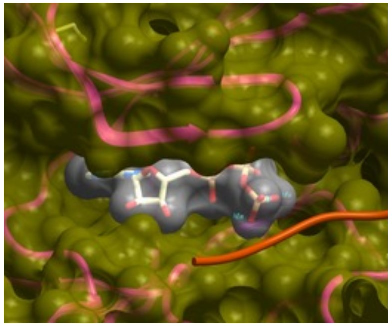
Equilibria and Kinetics of Processes Associated with Drugs

- **Crystallization, dissolution, diffusion, osmosis, effusion, permeation, state transitions, chemical and conformational transitions, dynamics, molecular binding and dissociation, elimination/accumulation**



Disciplines

- **Thermodynamics**
- **Kinetics**
- **Molecular Structure**



The Skaggs School of Pharmacy and Pharmaceutical Sciences

Ruben Abagyan, ©2023

Paul Jackson

Website: http://ruben.ucsd.edu

Learning Objectives

- Energy, Work, Pressure, Temperature, SI units, Gas Constant
- Tell from a drug structure *how many* molecules are in *X* g of substance, or in *Y* liters of gas
- Calculate a *kg-mass* of an individual drug molecule
- From molecular weight of a drug calculate at what *speed* a drug molecule is moving at any *T*
- Memorize the Avogadro number and the Gas constant
- Memorize the formula for kinetic energy and energy per degree of freedom of a mole of molecules
- Figure out the *units* of the gas constant
- Tomorrow: Gas Law, Barometric formula

Classifying and Naming Drugs

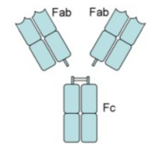
- **Therapeutic types** (physiological change), e.g.
  - Antihypertensive; Anticoagulants; ..
  - Antipsychotics; Hallucinogens; ..
- **Pharmacological types** (specific molecular mechanism of action), e.g.
  - Beta-adrenergic blockers; Calcium-channel blockers,..
- **Drug molecule type, size and properties**
- **Names**: **chemical** (e.g. (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid)
  - **generic (**e.g. Ibuprofen)
  - **brand name** (many), e.g. Advil, Motrin, .. Differences include:
    - Inactive ingredients; bioavailability; prices, ownership rights, etc.
- **Drug addiction/abuse potential, Controlled subst., Schedules**:
  - **I** (Heroin, LSD, marijuana, Ecstasy, ..) **II** (<15mg Hydrocodone, Fentanyl, Adderall, Ritalin)
  - **III** **(**<90mg of codeine, ketamine, testosterone, anabolic steroids)
  - **IV** (Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Ambien, Tramadol,..)
  - **V** (limited quantities of narcotics, cough preparations, etc.)

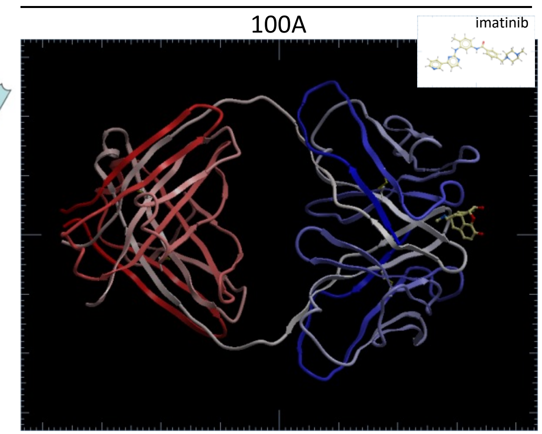
How big are drugs ? Physical Dimensions

SI unit for size: a meter

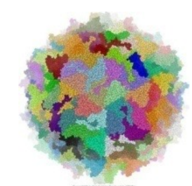
Ångströms and nanometers:

- **1Å = 10^{-10} m** and 1nm = 10^{-9} m = 10 A
- Interactomic distance C-H ~ 1A, C-C ~1.5A
- Small Drugs: from **5Å to 25Å** (PROTACs are larger)
- Drugs from natural products : up to **10Å - 35Å**
- Diameter of DNA : **20Å**
- Protein Drugs, antibodies, drug targets: **50Å to 100Å**
- Biological Membrane **60Å** with proteins up to **100Å**
- HIV virus ~ **1000Å** = 100nM (0.1 µm)





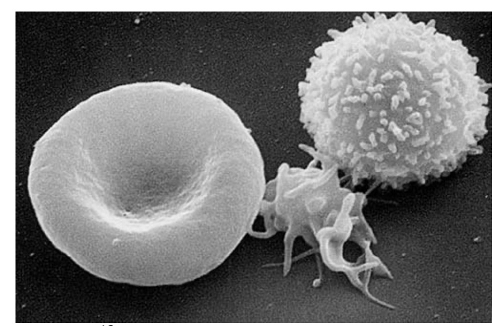
Morphine ~ 5A, Antibody Fab ~ 100A



Poliovisrus (x100)

Microns , µm = 10^{-6}m:

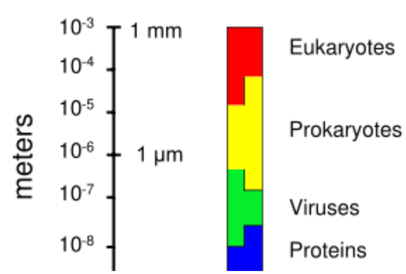
- Bacteria 1-10 µm visible in microscope
- Red Blood Cell ≡ nucleus of typical eukaryotic cell: 6-9 µm



2-3 x 10^{13} erythrocytes in human body
5-6K in 1mm^3 (4–11K white blood cells, 150–400K platelets)
Each with 270 million hemoglobin molecules
7.5 to 8.7 µm in diameter and 1.7 to 2.2 µm in thickness

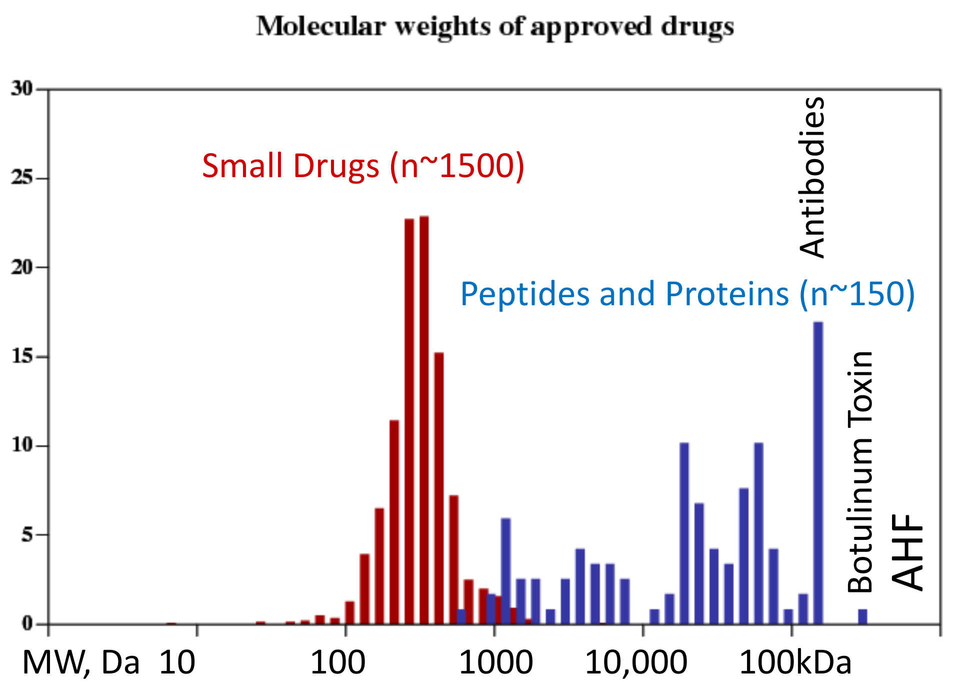
Anders Jonas Ångström

1814-1874, measured wavelengths of light in Aurora Borealis spectra



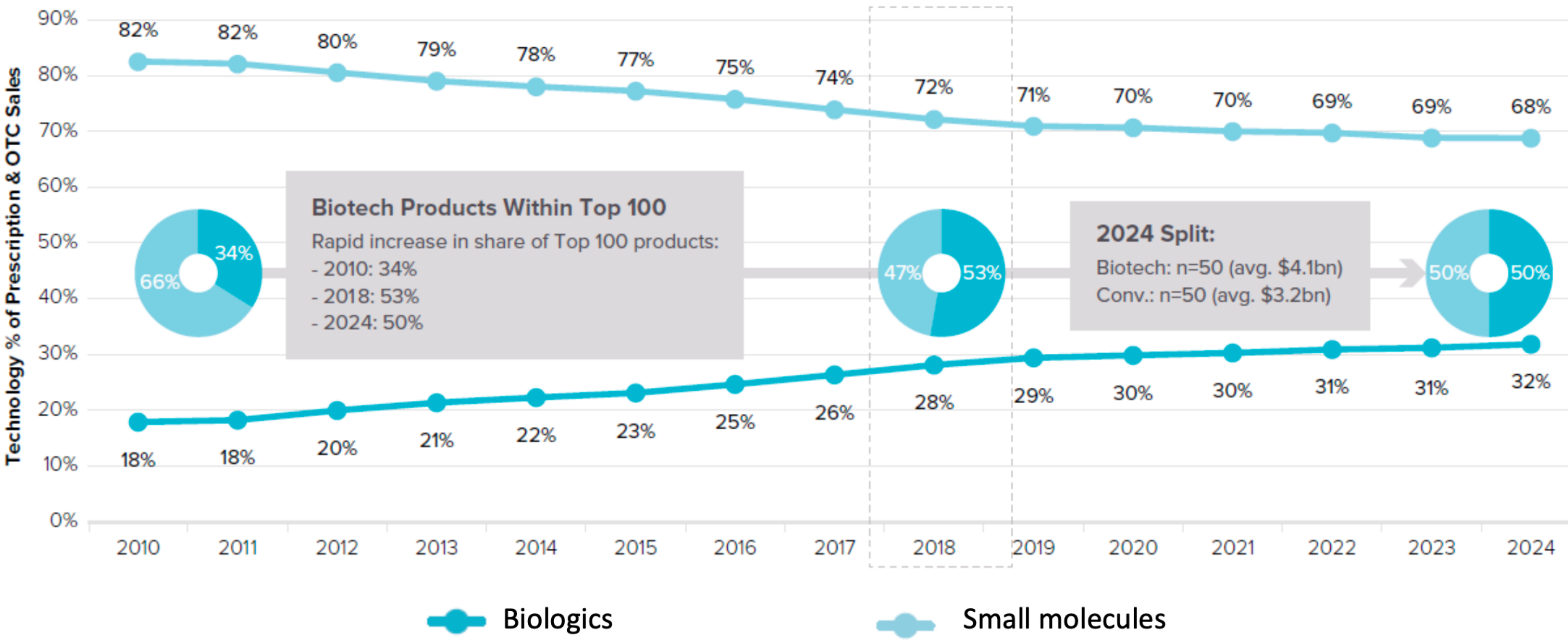
Sizes of drugs by MW: the extremes

- The smallest drug is noble gas Xenon **(Xe):** just one atom, but relatively heavy (131Da, or 131g/mol). It is used as an anesthetic. **Lithium** is even smaller active ingredient.
- Nitrous Oxide, **N_2O** (44 Da) is colorless gas, used for euphoria, sedation, pain relief. Inhaled.
- The largest single molecule drugs are proteins (~150 kDa for IgG). **Assemblies** may include viral (-like) or **nano particles**, . Human recombinant anti-hemophilic factor (AHF) or Factor VIII, 2332 residues, glycosylated, produced by insect cells



Biologics (biopolymers) move up but are still a minority

Worldwide Drug Sales: Biologics vs. Small molecule



Administration: Par**enteral** (IM, IV, SQ,..)
Cost: high

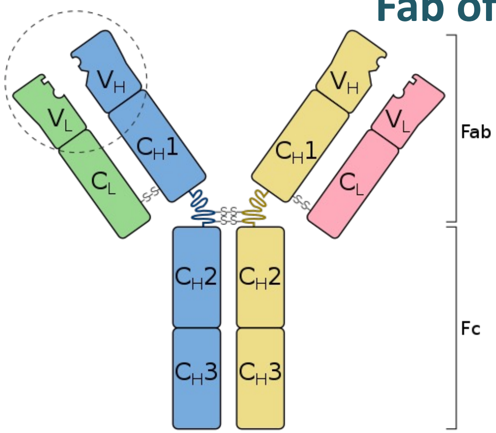
Credits: Anthony O'Donohue, 263A class
EvaluatePharma World Review 2019

EUAed Covid19 antibodies: Tixagevimab + Cilgavimab (EVUSHELD^{TM}), EUA
Previously EUAed: casirivimab plus imdevimab, sotrovimab, and bebtelovimab not active against Omicron subvariants

Large Drugs: Spike Antibodies

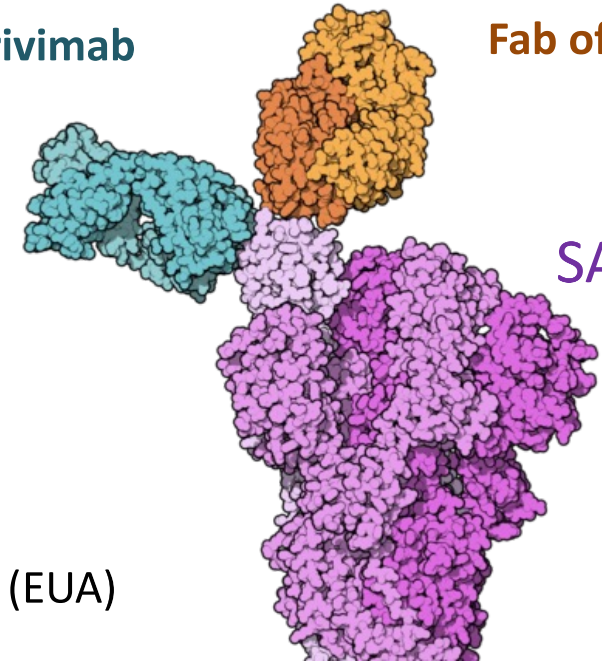
Casirivimab + **Imdevimab**

Fab of Casirivimab



Regeneron antibody cocktail, Emergency use authorization (EUA) on Nov 21st, 2020

Fab of Imdevimab



SARS-CoV2 Spike Protein

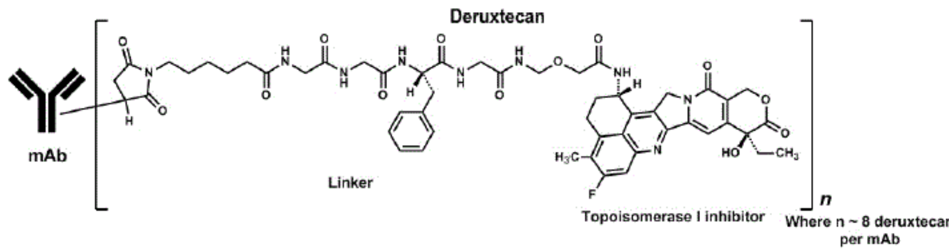
PDB: 6VSB, 5XDG

Large and New: **Antibody-Drug conjugates** and Vaccines

- Antibody-drug-conjugate (ADC)

  Dec 2019: Enhertu : HER2-directed-ADC vs metastatic breast cancer

  Monoclonal Antibody
  Trastuzumab



- Sars-CoV2 vaccines
  - Pfizer (mRNA)
  - Moderna (mRNA)
  - CovonaVac (from Sinovac)
  - ..

Wisconsin pharmacist, 46, ruined hundreds of doses of Moderna's COVID-19 vaccine 'because he thought they were unsafe'

Steven Brandenburg, 46, was arrested in Wisconsin last week following an investigation into the 57 spoiled vials of the Moderna COVID-19 vaccine

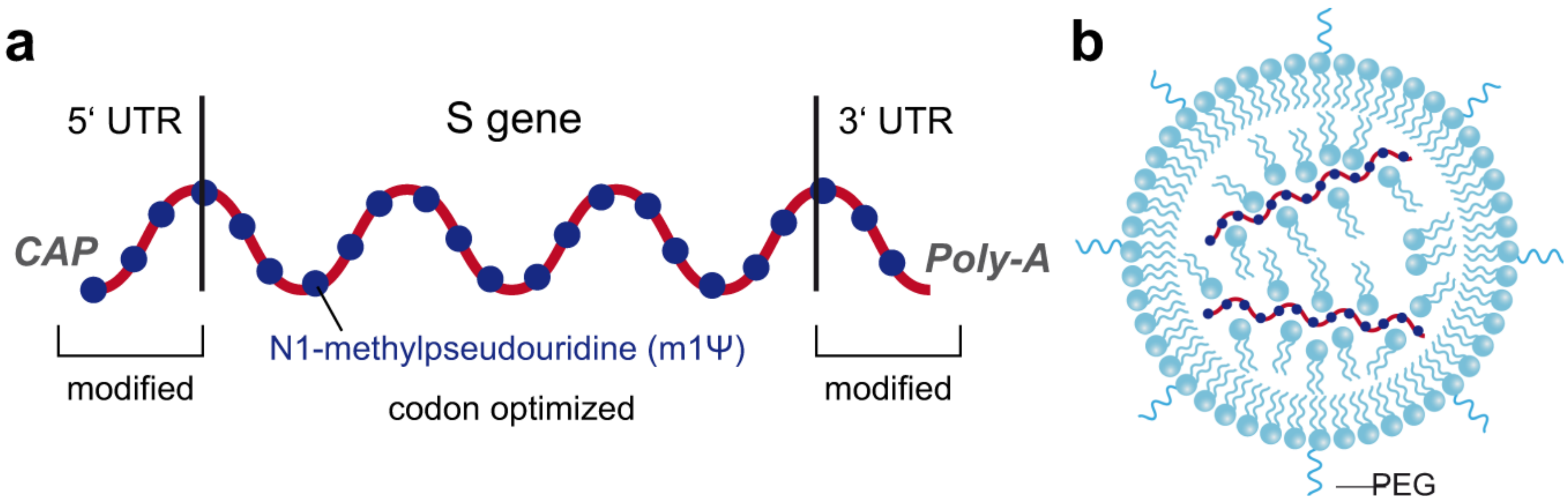
Share 1.4k 227 comments 1 video

Ref: F.Krammer, Nature, 2020, SARS-CoV-2 vaccines in development

Moderna and Pfizer Rna Vaccines in LipidNanoParticle

Composition: LNP of several lipids, PEG, RNA

Size: sub-micron, < 1μm



UTR—untranslated region. **b** Schematic of a lipidnanoparticle (LNP) used for delivery of mRNA vaccines. PEG—polyethyleneglycol

Credit: Heinz, F.X., Stiasny, K. Distinguishing features of current COVID-19 vaccines: knowns and unknowns of antigen presentation and modes of action. *npj Vaccines* **6**, 104 (2021). https://doi.org/10.1038/s41541-021-00369-6

Drug Giants: **Luxturna**: Viral carrier + Gene

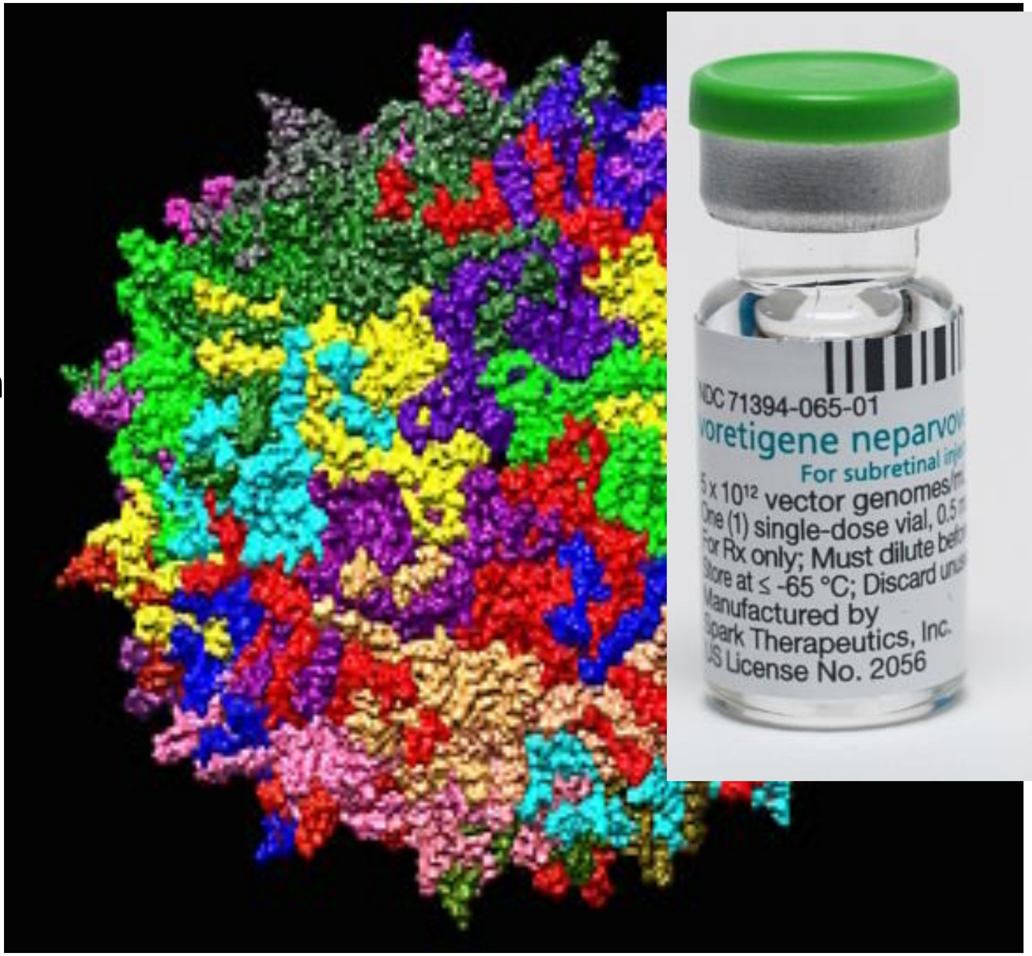
First FDA approved gene therapy:
Luxturna (Spark Therapeutics),
a.k.a. **voretigene neparvovec-rzyl**

Disease class:
Inherited retinal dystrophies (IRDs)
mutations in one of 220 genes
one of frequent offenders: RPE65

Drug: Adeno Associated Virus 2 vector with RPE65 gene (AAV2-RPE65)

Approval: 2017, 27 out of 29 gained vision

Price tag: $850,000 per one treatment



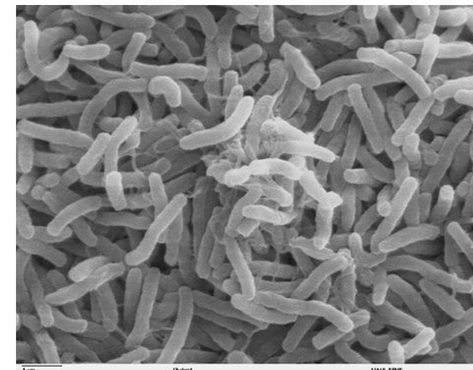
AAV2 virus: icosahedral (12v, 20 faces)
60 proteins: VP1,VP2, VP3,

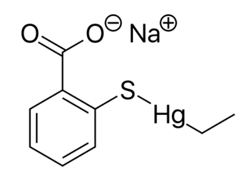
Capsid MW: 3.9 Mdaltons (>300K C)
Subretinal injection

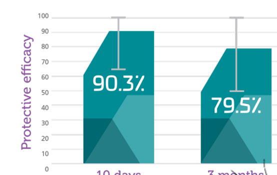
Also:
Kymriah/(tisagenlecleucel) 2017, CAR-T for leukemia:
Vaccines, Cell therapies, Crispr/CAS9 for gene editing,
Fecal Transplants, parasitic worms in helminthic therapies

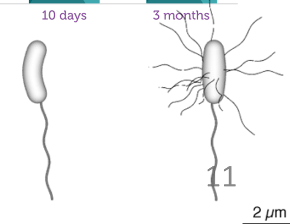
Large and Complex Pharmaceuticals: **Cholera Vaccine** (Vaxchora, FDA appr. 2016)

- Single-dose oral cholera vaccine
- Targets predominant *Vibrio cholerae* serogroup O1
- Makes an incomplete, nontoxic "toxin".
- V. Cholera : ~4000 genes, DNA 4M base pairs
- Excipients in other vaccines (from CDC site)
  - flu/Afluria vaccine: beta-propiolactone, **thimerosal** (multi-dose vials), monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, neomycin sulfate, polymyxin B, egg protein, sucrose
  - MMRV (Measles, Mumps, Rubella, and Varicella) Vaccine: sucrose, hydrolyzed gelatin, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium phosphate dibasic, neomycin, bovine calf serum, chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells









How many molecules in 1 mole?

- **Avogadro** number N_A (rule of 6) =2x3

$$6.022 \times 10^{23}$$

n_{moles} [mol] = ***Mass*** [g]/***MolWeight*** [g/mol]

What contains N_A molecules?

- 1 mole of anything (tautology)
- 12g of carbon
- *(Molecular Weight in atomic units)* grams of any substance
- ~22.4 liters of any gas at 273.15K and 1atm

One mole of substance ≡ Avogadro number of substance molecules.

Amedeo Avogadro (1776-1856), Torino, Italy. Count of Quaregna and Cerreto

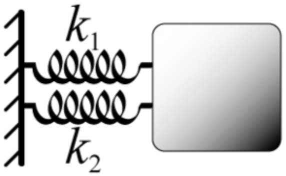
In 1811, hypothesized that equal volumes of gases contained equal number of molecules. N_A is a.k.a. Loschmidt's number. Josef Loschmidt and Jean Baptiste Jean Perrin gave increasingly accurate estimates of N_A

Energy : Main Entity in Physics and Chemistry

- **Ability of therapeutics to affect bio molecules is defined and guided by energy balance.**
- **Energy** ≡ capacity to do work

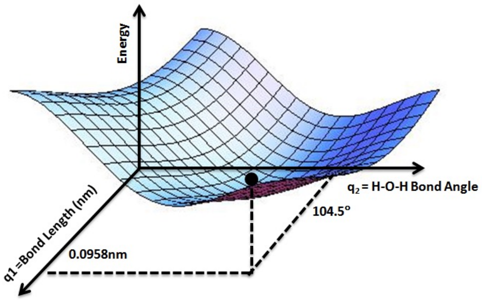
- The **kinetic energy**, E_k of a body is the energy the body of mass ***m*** possesses as a result of its *motion* at speed ***v*** is.

$$E_K = \tfrac{1}{2}mv^2$$



$E_P = \tfrac{1}{2}kx^2$

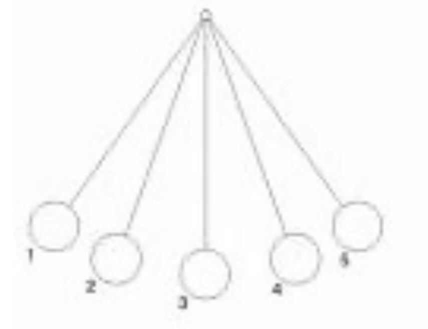
- The **potential energy**, E_p , is a result of its *position*, *composition* or *condition*. Drugs: electrostatic energy, other interaction types,



- Only energy ***difference*** makes physical sense.
  For that reason the position at which the potential energy is *zero* is arbitrary (e.g. infinite separation of two charges).

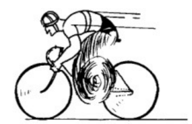
Conservation of Energy

Kinetic Energy + Potential Energy
Movement (K) + Position (P)



$$E_{total} = E_K + E_P$$

- **The total energy is conserved**
- The total energy can be changed
  Work ≡ Force • Distance

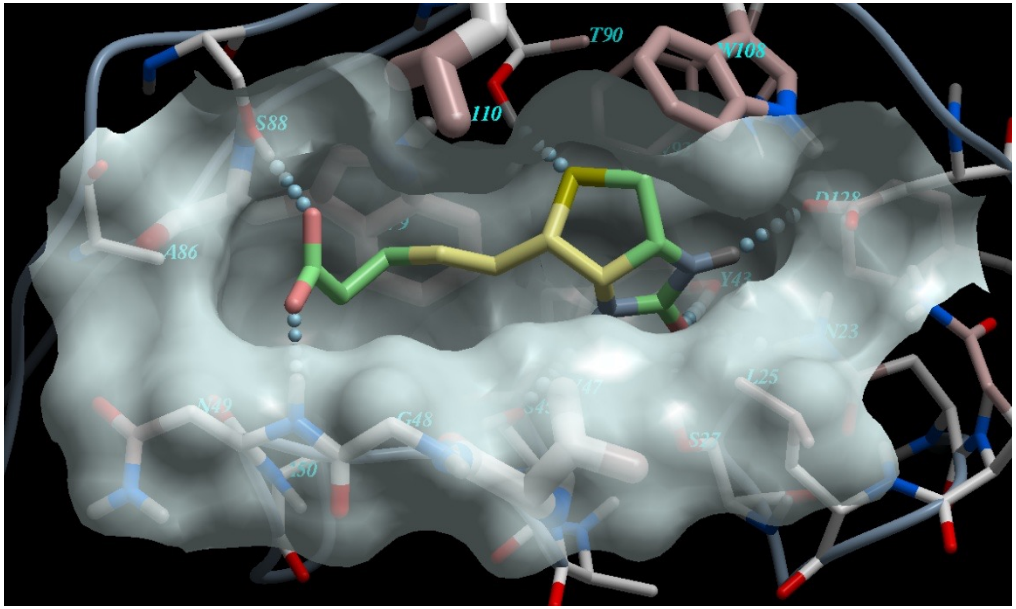


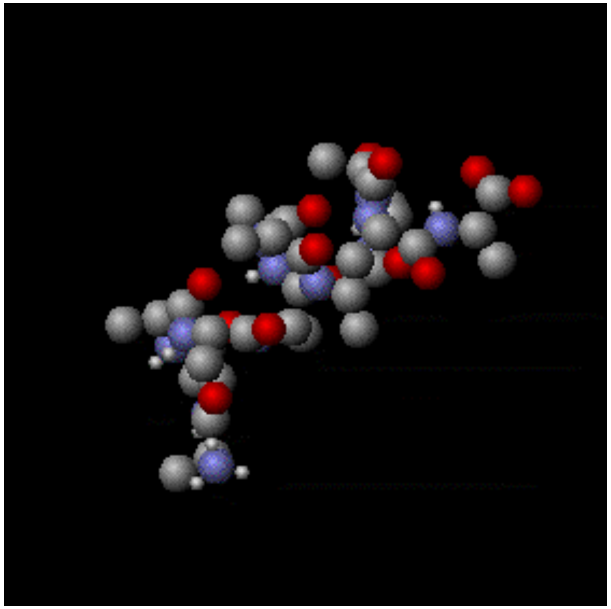
- What happens when a cannon ball is dropped ?
- **Temperature** is the average energy of random molecular movements per degree of freedom

Gottfried Wilhelm Leibniz
1646-1716 , Germany,
vis viva , living force,
conservation of energy

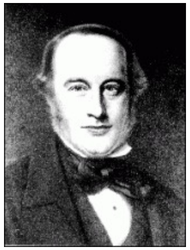
Seeking a minimum of energy

- Every *mechanical* system *with dissipation* seeks to achieve a **minimum** of potential energy within constraints





Energy Units



James Prescott **Joule**

1818-1889

English physicist and brewer

- The SI units: kilogram, meter, second
- The SI unit for energy is **Joule**.

$$J = kg\ m^2\ s^{-2} \quad (E_K = ½mv^2).$$

- **Calories** are also used as a measure of energy. One calorie is the energy needed to increase the temperature of 1 gram of water by 1° C.

$$1\ cal \approx 4.184\ J$$

$$1\ kcal \approx 4.184\ kJ$$

(beware of the food Calories!)

- **Electron-volts (eV)**:

$$1\ eV = 1.602176565 \times 10^{-19}\ Joules$$

Temperature : Energy **Equipartition** in thermal equilibrium

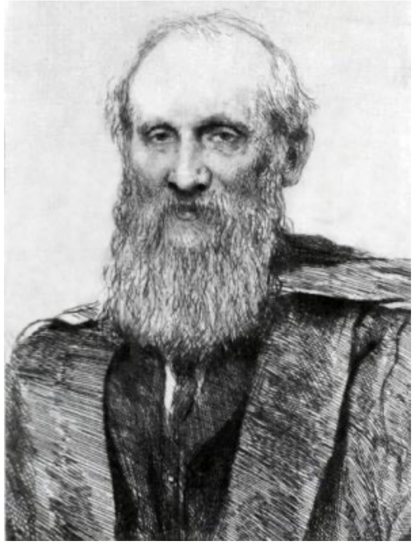
- Absolute temperature is a measure of energy per degree of freedom
- Every excited *degree of freedom* of one molecule in a mixture carries energy is proportional to the **Absolute** temperature (Kelvin, K)

$$e_{DF} = ½\, k_B T$$

- For $N_A = 6 \bullet 10^{23}$ molecules,

$$E_{mole\_of\_DF} = ½\, RT$$

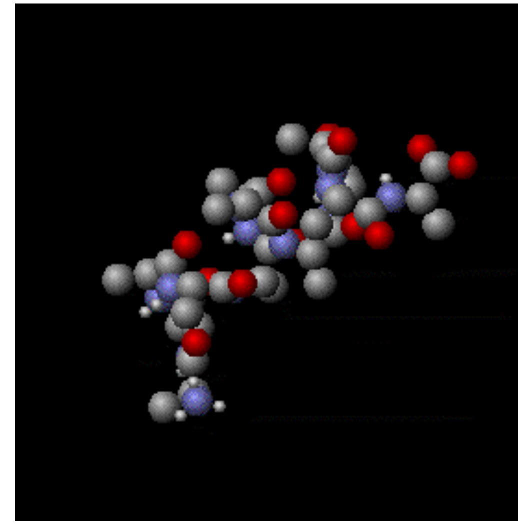
- R is the universal gas constant

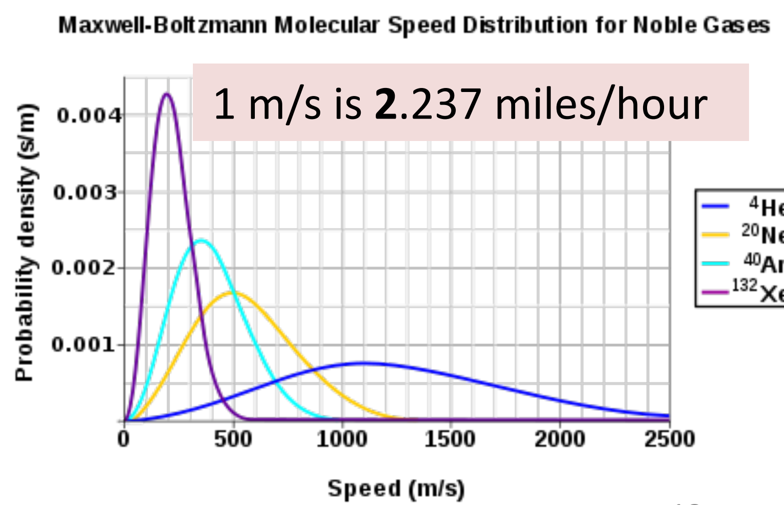


William Thomson, Lord Kelvin ***1824-1907 UK***
In 1821 wrote "On an Absolute Thermometric Scale". Coined the term "thermodynamics"

Counting Degrees of Freedom

- For Molecules in Gas:
  - External DF: **6**=3+3
    - 3 one atom, 5 for linear
  - Internal: from 0 to $3N_{at}$-6
- **Vibrations**: **One vibration = Two DFs**
  - Bond length
  - Bond angle
  - Torsion angle
- Vibrational DF may not be excited at room temperature
- More DFs are excited as temperature increases to reach a limit of 3N potential and 3N kinetic degrees of freedom in a crystal





1 m/s is **2**.237 miles/hour

Gas Constant and Kinetic Energy of a Molecule

- $R = 8.314$ J K^{-1} mol^{-1}
- Mnenonic device: $8.\pi$
- $R = 1.9872 \sim 2$ cal K^{-1} mol^{-1}
- For 3 translational degrees of freedom of movement of one atom in a gas:

$\pi \approx 3.14$

$A = \pi r^2$

$L = 2\pi r$

$\mathbf{E_{one\ atom\ in\ gas}}$ [J] **= 3/2 k_B T = 2. 10^{-23}** [J/K] **T** [K]

$\mathbf{E_{one\ mole}}$ [J] **= 3/2 R T = (1.5*8.314)** [J/K] **T** [K]**~13T**

Temperature units, k_B and R

- Kelvin (K): 273.15 + °C
- Celsius: °C = K - 273.15

(freezing and boiling temperatures of water are 0. and 100., body temperature 36.6°C)

- Fahrenheit : °F = °C·1.8 + **32**.

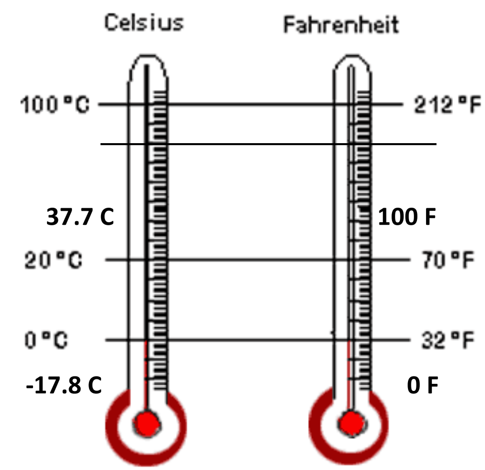
(human body temperature is 98.6, fever 100°F)

- We will work only in °C and °K

- $k_B = 1.38\ 10^{-23}$ J/K
- $R = k_B\ N_{Avogadro}$
- $R = 8.314$ J/(K mol)

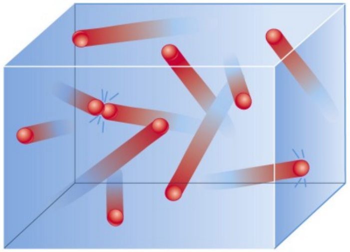
Anders Celsius, 1730

Daniel Gabriel Fahrenheit, 1724



Temperature defines internal energy of molecules

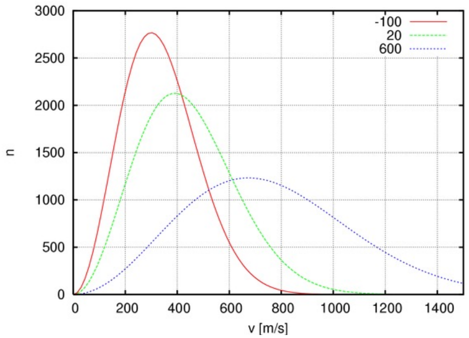
The mean energy of one mole of vibrations is **$R\,T_{Kelvin}$**



RT at 300K

0.6 kcal/mol

2.5 kJ/mol



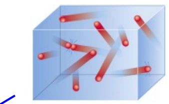
½ RT – thermal energy (kinetic,potential) per mole of one degree of freedom

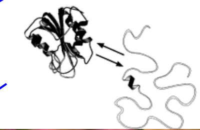
RT – in drug binding (or rate) constants all energies are divided by RT

3 (½ RT) – thermal energy of translational movement of a molecule

Energy Scale

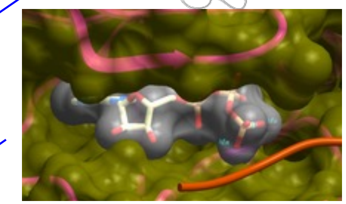
All numbers are per mole=N_A of particles
"One" means "One mole of"

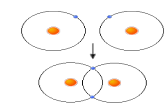




Energy in Joules or calories per mole of events

- 2.5 kJ 0.6 kcal one vibration at 300K
- 20-30 kJ 5-10 kcal Protein unfolding
- 40-60 kJ 10-15 kcal nanomolar drug binding
- 160-320 40-80 kcal visible light photons
- 300-700kJ 70-150kcal breaking a chemical bond
- 510 M kJ 120 M kcal alpha-particle. Polonium-210 has a half-life of 138 days and a decay alpha particle energy of 5.3 MeV.





- Reminder: 1 kcal : 1 kg of water by 1°, 1 bagel = 150 kc

- Energy of 1 particle is E/N_A

Mr. Litvinenko dying from Polonium 210 poisoning

SI and PChem Units

Unit	SI	Pharmacology	Comment
Length	m, Meter	Å, nm, μm, cm	
Temperature	K, Degree Kelvin	Celsius, K	Do not use F
Time	s, Second	s	
Mass	kg, kilogram	g = 10^{-3} kg, Da (Dalton), mg,μg	
Energy	J, Joule	kJ, kcal, Cal (?)	Do not use Cal
Substance	mole	mole	6.022 10^{23}
Volume	m^3	L = $10^{-3} m^3$, mL,	

Volume	Linear Size	Mass of water
1 m^3 (SI)	1 m	1 tonne (metric ton): 1000 kg
1 L	10 cm	1 kg
1 mL	1 cm	1 g
1 μL	1 mm	1 mg

Review

- SI units for length: meter
- Smaller units: **Å**, nm, μm
- Sizes of drugs, proteins, membrane, cells
- Mole, **Avogadro (6)**: $\mathbf{N_A \sim 6\ 10^{23}}$
- Kinetic energy = **½ $\mathbf{mv^2}$**
- Conservation of energy
- **Equipartition** & absolute T
- 1 mole (ie N_A) of degrees of freedom carries ½ RT, (1 has ½kT)
- Temperature: ½ mv^2 = 3/2 RT

- Celsius (**273.15**) and Fahrenheit
- Energy units: J, cal, kcal, Cal, eV
- **Gas constant (8.π)** **8.3**14 $JK^{-1}mol^{-1}$
- Boltzmann constant (R/N_A)
- **RT** at room temperature **0.6kcal/mol & 2.5 kJ/mol**
- Energies of drug binding, photon, unfolding
- 1 calorie = 4.184 Joules