Cancer Immune Modulator Therapeutics:

Advanced Computing Tools

Jack D. Hidary

AQ = AI + Quantum Info Sciences

Bits:

We can generate, store, and transmit bits better and better,

AI = bits manipulation on bits

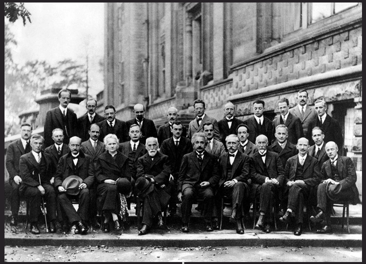
Quantum Information Sciences

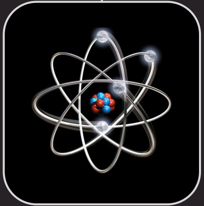
- Physics, Chemistry, Maths, Engineering
  - Drug Discovery
  - Battery Chemistry
  - non-Silicon based semiconductors

We are now in the 3rd quantum revolution

1st Quantum Revolution

Understanding and Predicting physical processes at the Quantum level, from Theory to the Lab





1st Revolution
Quantum Mechanics: Theory and Foundations

2nd Quantum Revolution

2nd Revolution Innovations:
Transistors, MRI, Lasers, and other 2nd Rev breakthroughs created large markets and opened up new platforms for innovation.

3rd Quantum Revolution

Engineering Quantum Systems

Simulation & Optimization

Sensing

Security & Communication

3rd Revolution
Engineering at scale

SANDBOXAQ™

2nd quantum revolution tech

We can leapfrog this technology for even greater impact

Transistor

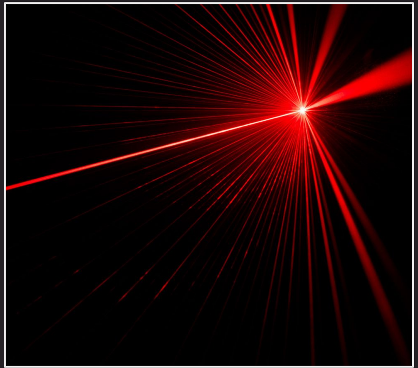
In 1947, physicists Bardeen and Brattain developed the transistor, through the quantum-level phenomenon of a semiconductor band gap.

Today quantum-driven transistors make up the basis of computing, changing the way people communicate, work, and live.

MRI

In 1977 physician Raymond Damadian conducted the first human MRI scan, leveraging a quantum-physics based technique of nuclear magnetic resonance for imaging.

Today, quantum-driven MRIs have decreased mortality through improved diagnosis and treatment.



Laser

In 1960 Physicist Ted Maiman developed the laser, leveraging quantum physics.

Today, quantum-driven lasers have the changed the way we store, observe, and separate data from music to light to weapons, to astrophysics.

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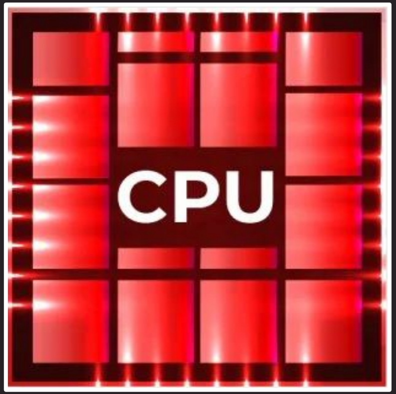
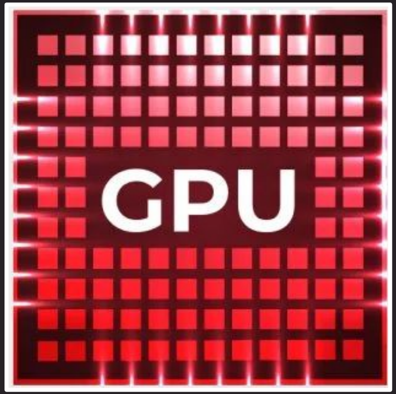
GPUs have revolutionised modern computing



- CPUs have few larger cores
- Designed for general computing and management of compute processes



- GPUs have thousands of smaller cores
- Focused on operations of matrices in parallel
- AI, Video Games

DIFFERENCE BETWEEN CPU AND GPU ARCHITECTURE

Development driven by intense competition

AMD
Alphabet
amazon
intel
ASUS
GRAPHCORE
NVIDIA

Over 10x teraFLOP increase in last 10 years driven by intense competition

GPU development from gaming to AI

Over 10x teraFLOP increase in last 10 years

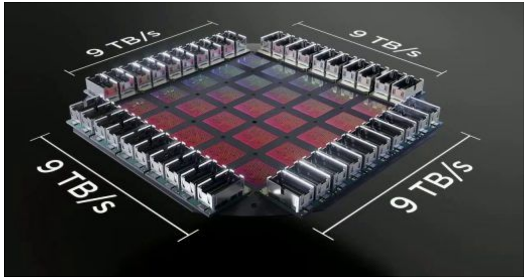
Gaming
Arcade boards & display adapters

First GPU
GeForce256

NVidia TESLA V100
Tensor Core GPU

Latest large AI models are all run on large arrays of GPUs

Stable Diffusion, Big Science etc…

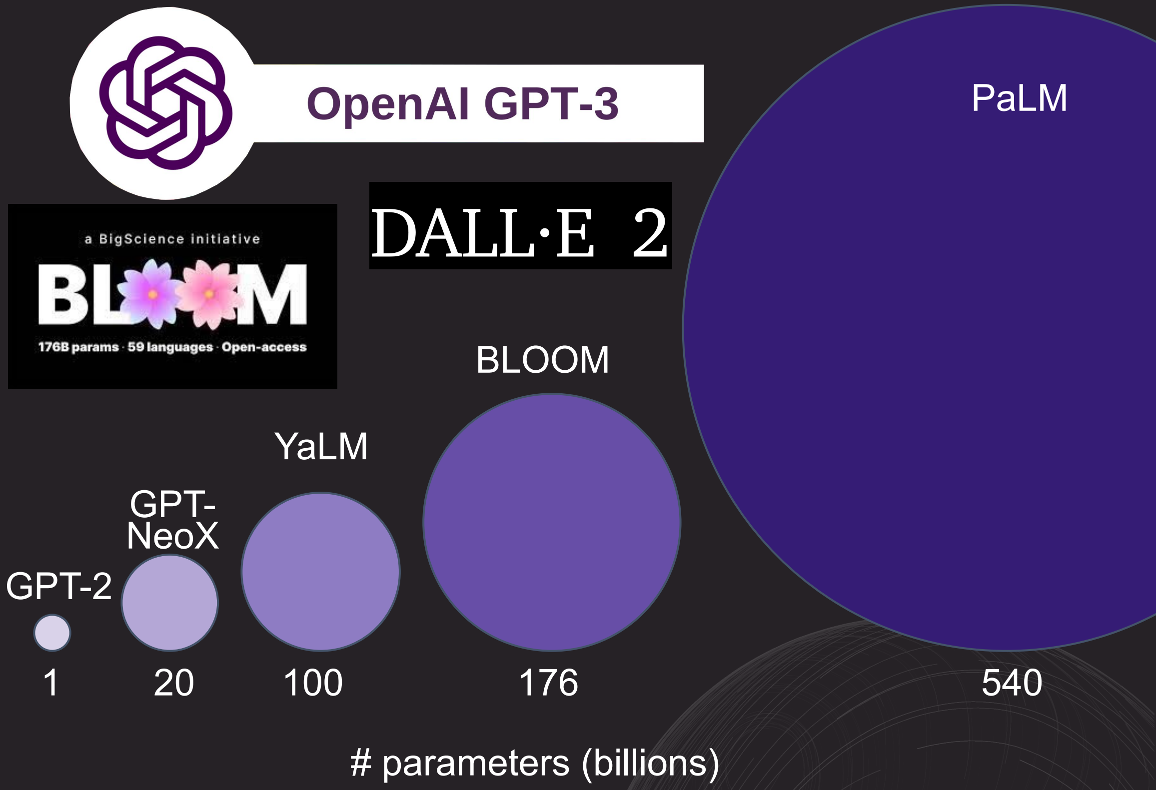


Tesla D1 chip

GPU supercomputer

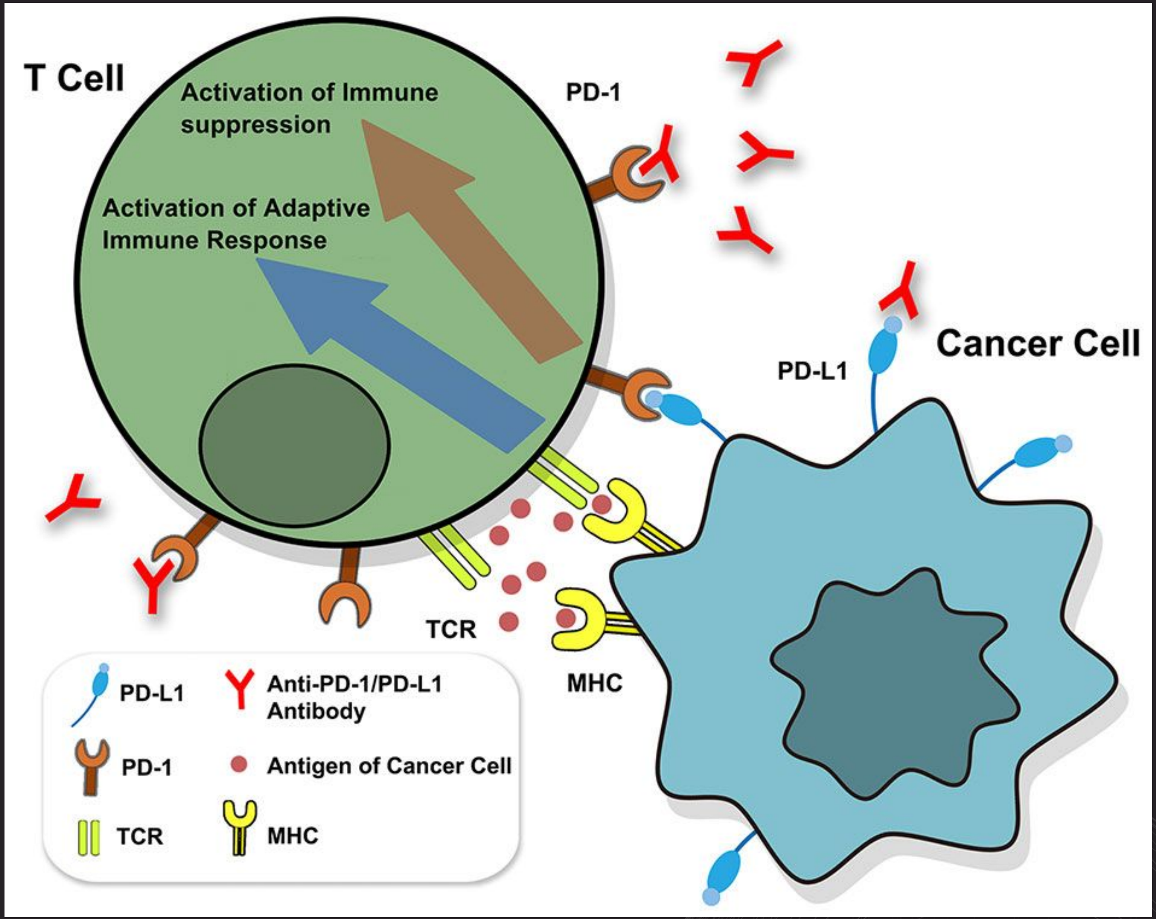
Large Language Models now possible with newer GPUs

- New generation of NLP (Natural Language Processing) models
- Based on the Transformer architecture developed at Google
- Billions of parameters are trained on hundreds of GB (costing millions of dollars)
- Pretrained models are meant to have wide applicability



$1-4 Billion	10-15 Years	87%
Cost to develop a drug	Time to develop for small molecules	Rate of drugs that don’t make it past clinical trial

Checkpoint Inhibitor Immunotherapies



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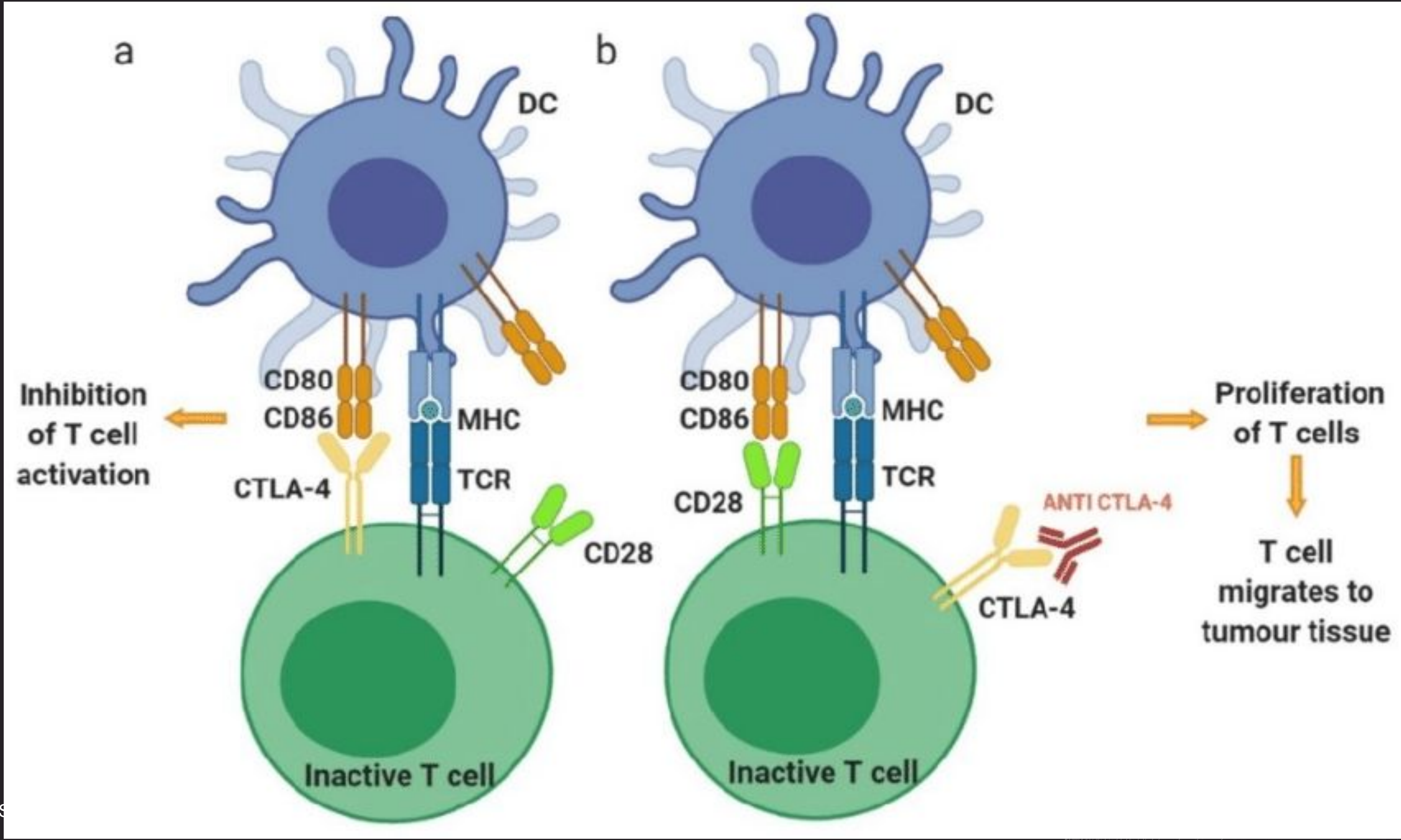
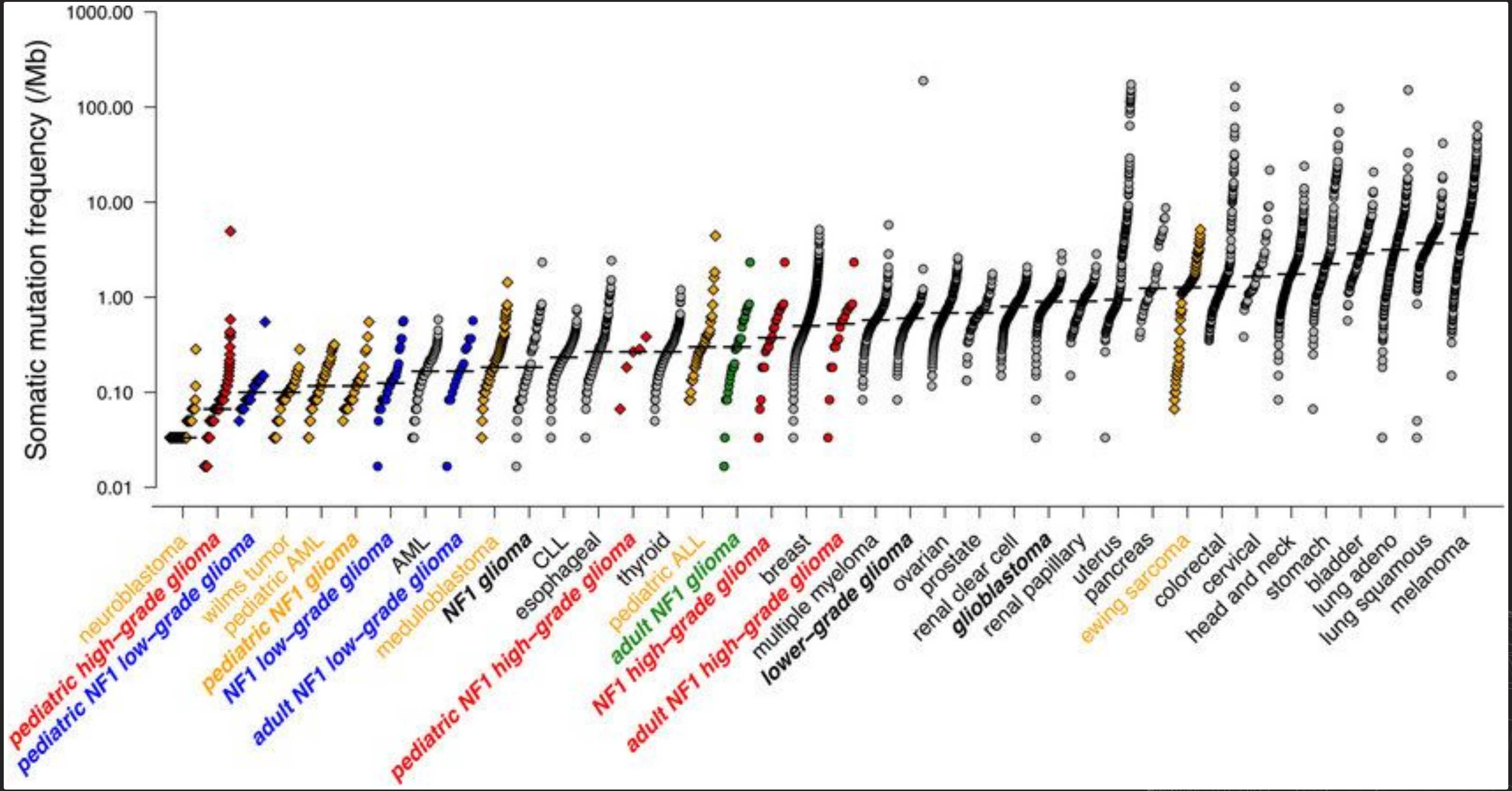

a
DC
Inhibition of T cell activation
CD80
CD86
MHC
CTLA-4
TCR
CD28
Inactive T cell
b
DC
CD80
CD86
MHC
TCR
CD28
ANTI CTLA-4
CTLA-4
Proliferation of T cells
T cell migrates to tumour tissue
Inactive T cell

Approved immunotherapies

A sample of FDA-approved cancer immunotherapies:

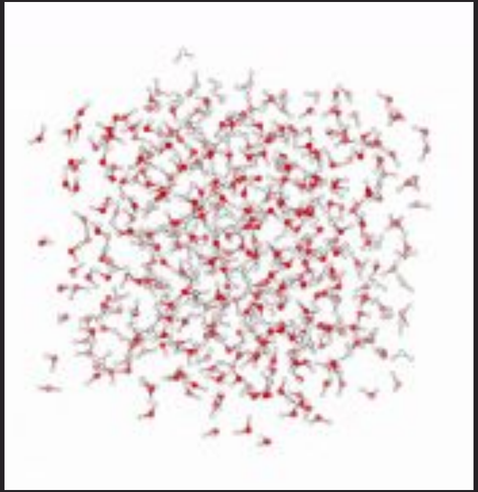
- ipilumumab - late-stage melanoma + other cancers
- nivolumab - late-stage melanoma + other cancers
- sipuleucel-T - prostate cancer
- blinatumomab - lymphoblastic leukemia
- pembrolizumab - non-small cell lung cancer
- brentuximab vedotin - classical Hodgkins lymphoma

Tumor Mutation Burden (TMB)



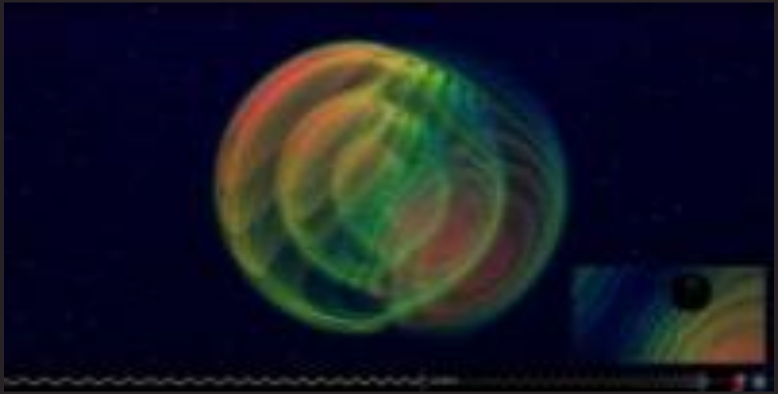
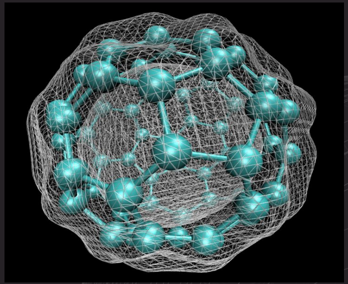
Checkpoint Inhibitor - combination therapy challenges

- Nivo and Pembro have about a 32% durable response in melanoma; less so in other cancers
- **There have been more than 270 trials for combination therapies with only few successful trials**



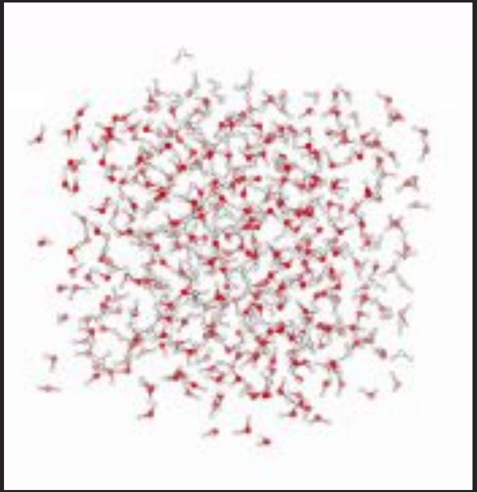
Quantum Simulation & Quantum Physics

- Computers can simulate physics and when they do, computers behave like the physical world.
- Simulating *quantum* physics is needed in drug discovery because electrons are quantum.
- This introduces extra complications which we solve using modern HPC and GPU computing.

How can accurate quantum models improve protein simulations asynchronously?

- We assemble a **database** of quantum electronic simulations **in advance**.
- **Machine learning** then brings **quantum accuracy** to e.g. protein/ligand simulations.
- The database **actively improves** in **response to your needs**.
- The database is **agnostic** about how it was constructed.
  - You **seamlessly** benefit from advancing technology.
  - **For now we get power from a combination of GPUs, TPUs, and HPC as needed**.



Quantum Simulation on Classical Computers

Simulation of quantum physics with Tensor Processing Units: brute-force computation of ground states and time evolution

Markus Hauru,[1] Alan Morningstar,[2,1] Jackson Beall,[1] Martin Ganahl,[1] Adam Lewis,[1] and Guifre Vidal[1]
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(Dated: November 23, 2021)

Large Scale Distributed Linear Algebra With Tensor Processing Units

Adam G.M. Lewis,[1] Jackson Beall,[1] Martin Ganahl,[1] Markus Hauru,[1] Shrestha Basu Mallick,[1] and Guifre Vidal[1]
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(Dated: December 17, 2021)

Density Matrix Renormalization Group with Tensor Processing Units

Martin Ganahl,[1,2] Jackson Beall,[1,2] Markus Hauru,[2,3] Adam G.M. Lewis,[1,2] Jae Hyeon Yoo,[2,4,5] Yijian Zou,[2,6] and Guifre Vidal[2,4,7]
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[6] *Stanford Institute for Theoretical Physics, Stanford University, Palo Alto, CA 94305, USA*
[7] *Google Quantum AI, Mountain View, CA 94043, USA*
(Dated: April 13, 2022)

Tensor Processing Units as Quantum Chemistry Supercomputers

Ryan Pederson,[1,2,3] John Kozlowski,[4,2,3] Ruyi Song,[5,2,3] Jackson Beall,[3] Martin Ganahl,[3] Markus Hauru,[3] Adam G.M. Lewis,[3] Shrestha Basu Mallick,[2,3] Volker Blum,[5,6] and Guifre Vidal[2,3,7]
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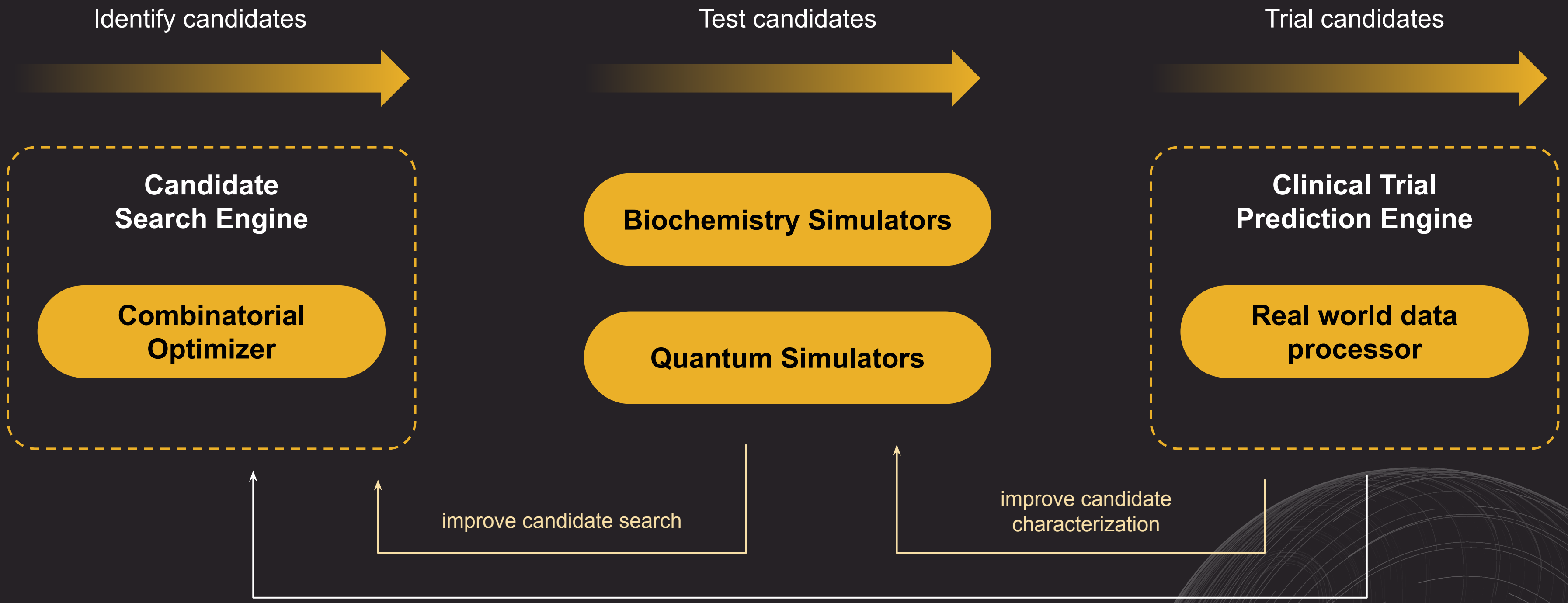
[7] *Google Quantum AI, Mountain View, CA 94043, USA*
(Dated: March 9, 2022)

- Qbit simulation
- Large-scale HPC
- Materials simulation
- Chemistry Simulation

Quantum Molecular Simulations + AI can help in three different entry points

Early Stage *Lead Optimization*	**Mid-Stage** *Clinical trial design*	**Late-Stage** *AI, ML & Simulation*
• Your target structure, or start with Alphafold • Refine lead data or start from scratch • Improved leads and docking scores using AQ protein/ligand interaction models. ○ Other biomolecular contexts (RNA, antibody…) also possible • Multi-parameter optimization of other drug properties	• Start with RWE insights to optimize Phase II trials • Find the right sub-populations with AI	• Multi-channel AI models combine RWE analytics with physics-based simulation. • Elucidates promising combinations and new indications. • Our models find these from RWE, and test them automatically *in silico*.

Simulation and AI can address the full drug discovery process



GUIDANCE DOCUMENT

Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products

FDA

Draft Guidance for Industry

DECEMBER 2021

EHR's led to approvals

Pfizer

U.S. FDA Approves IBRANCE® (palbociclib) for the Treatment of Men with HR+, HER2- Metastatic Breast Cancer

AstraZeneca

New data from landmark CVD-REAL study of patients with type-2 diabetes confirms CV benefits associated with SGLT-2 Inhibitors

What is Real World Data (RWD)?

RWD captures a patient's experience through:

- Their interactions with a healthcare system
  e.g. claims data, electronic health records(EMR)
- Data collected via surveys, registries, or wearable sensors

These datasets often contain:

- Diagnoses (ICD9/10 codes)
- Laboratory data
- Imaging
- Prescriptions
- Activity (wearable sensors)
- Quality of life (registries or patient reported outcomes/surveys)

Intersection of RWE & Simulation

Benefit: Combo-therapies & cost-effective variants

- RWE data inform novel combinations / indications
- Simulations can confirm findings at the molecular level.
- Increased clinical trial confidence

Perspective:

- Key opportunity is to move the RWE earlier into pipelines

Case Study RWE

nature

SCIENTIFIC REPORTS

Check for updates

OPEN

Post-vaccination outcomes in association with four COVID-19 vaccines in the Kingdom of Bahrain

Manaf AlQahtani[1], Xing Du[2], Sujoy Bhattacharyya[3], Abdulla Alawadi[1], Hamad Al Mahmeed[1], Jaleela Al Sayed[1], Jessica Justman[4], Wafaa M. El-Sadr[4], Jack Hidary[5] & Siddhartha Mukherjee[3]

With the emergence of new SARS-Cov2 variants, critical questions have arisen about: (1) the effectiveness of the available COVID-19 vaccines developed to protect against the original Wuhan (wild type) variant and (2) the magnitude and clinical consequences of post-vaccination infections in the context of the Delta variant of SARS-Cov2. While some "real world" experiences with various vaccines have been reported, to our knowledge, few have examined comparative outcomes of various vaccines in one country as new SARS-CoV-2 variants have emerged. Here we present an analysis of COVID-19 related outcomes from a national database in Bahrain, a country with a total population of 1.51 million, where four vaccines were deployed (total vaccinated = 1,003,960 adults): AstraZeneca (AZ/Covishield), Pfizer/BioNtech, Sinopharm and Sputnik V. We compare the four vaccines, based on the following post-vaccination outcomes: SARS-CoV-2 infections, hospitalisations, ICU admissions and deaths, compared to unvaccinated individuals. We conclude that the four vaccines used in Bahrain were effective in significantly reducing all four COVID-19 related outcomes compared to unvaccinated individuals, prior to, and during the period when the Delta variant predominated in the country. However, compared to the three other vaccines, individuals vaccinated with Sinopharm vaccine had a higher risk of post-vaccination infections, hospitalisations and ICU admissions (e.g., 6.94%, 2.24%, 1.99% and 1.52% of COVID-19 cases of Sinopharm, Sputnik V, Pfizer and Covishield recipients, respectively, required hospitalisation versus 13.66% of COVID-19 cases among unvaccinated individuals); however, given the confounding factors, this needs to be confirmed by further studies. We find no evidence of biased selection for any vaccine, but note waning protection of the Pfizer/BioNtech vaccine during the January to June 2021 period in the age > 60 y cohort; however, this cannot be distinguished from the overall fall in hospitalisations overall. Our findings support the value of vaccination in preventing COVID-19 related outcomes, provide real world estimates on the outcomes and frequencies of post-vaccination infections for the four vaccines, which may inform vaccine selection in the context of the Delta variant across the globe.

Highlights:

- Nationalized health system
- Anonymized EMR data for Covid-19
- Delta Variant outcomes-
  - stratified post-vaccination infections, hospitalisations and ICU admissions for Sinopharm, Sputnik V, Pfizer and Covishield recipients (6.94%, 2.24%, 1.99% and 1.52%)
- Helps inform future vaccine selection in other countries

https://www.nature.com/articles/s41598-022-12543-4

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Advanced Computing Tools

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