

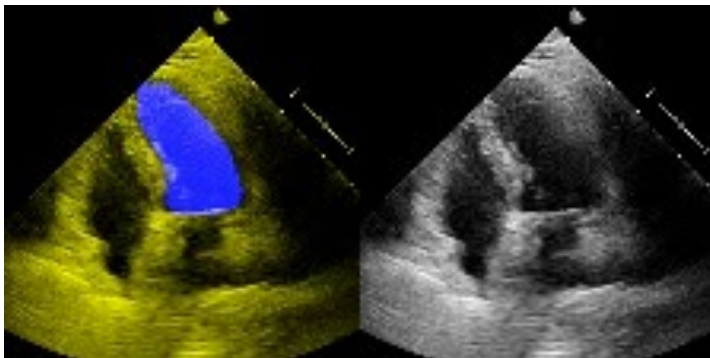
The Virtual Lab of AI Scientists

James Zou



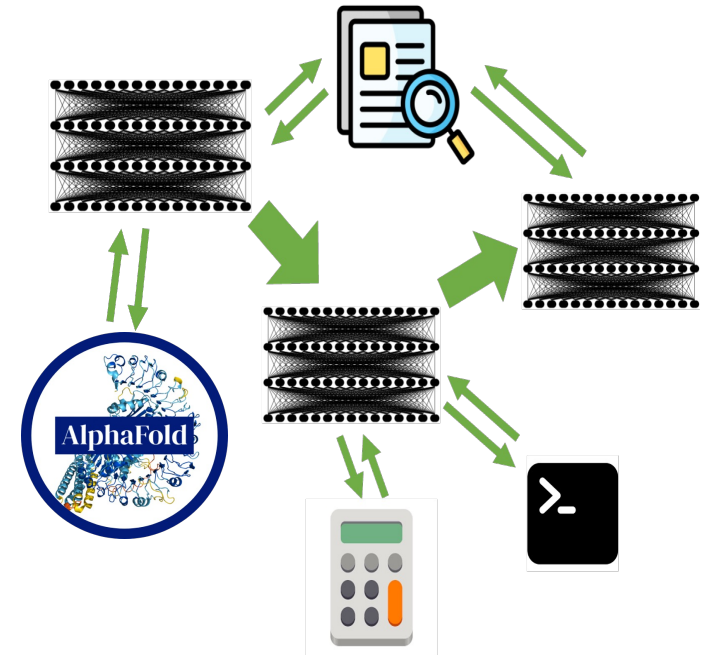
AI as a **tool** vs AI as a **teammate**

AI tools



EchoNet

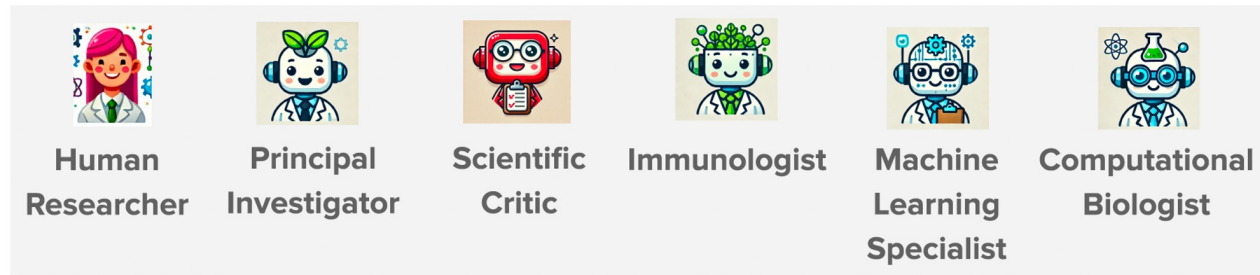
AI teammate



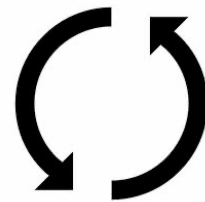
The Virtual Lab

The **Virtual Lab** is a team of interdisciplinary AI scientists that work with human scientist on challenging, open-ended research/development.

AI scientists



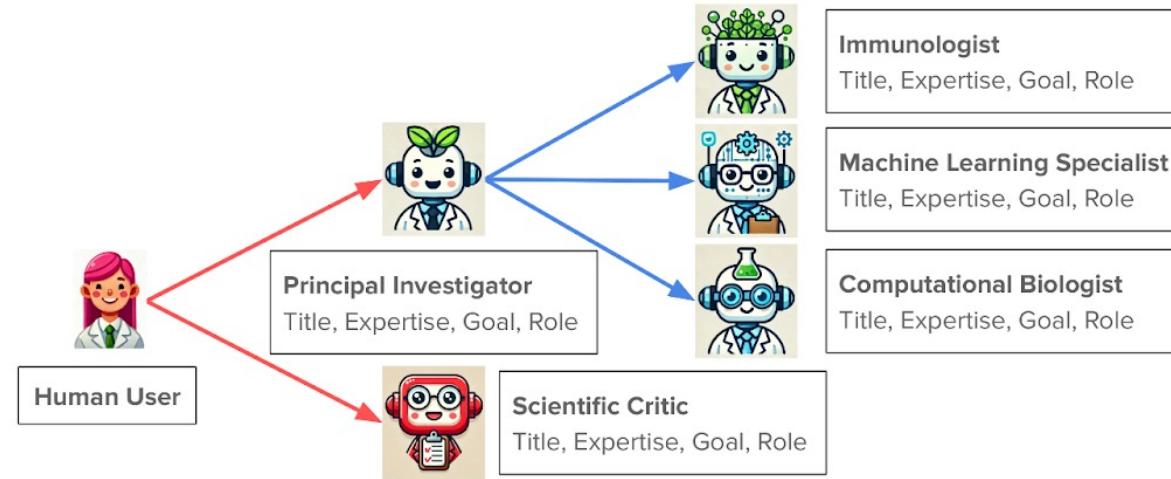
Self-learning agents



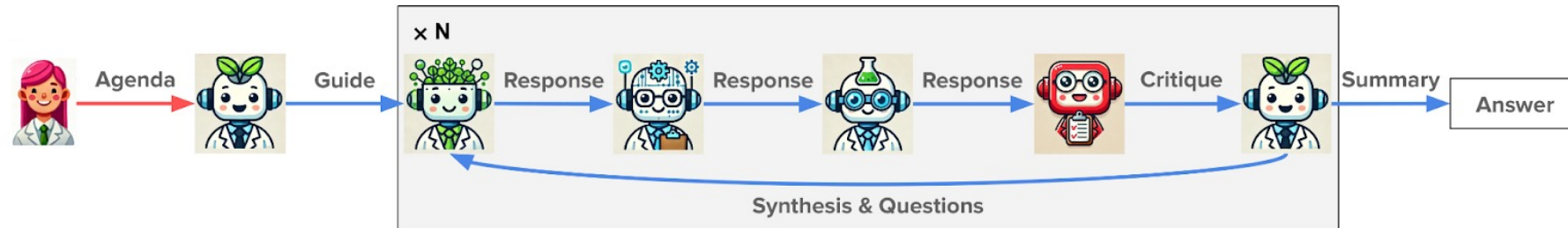
Virtual Lab School

Virtual Lab Design

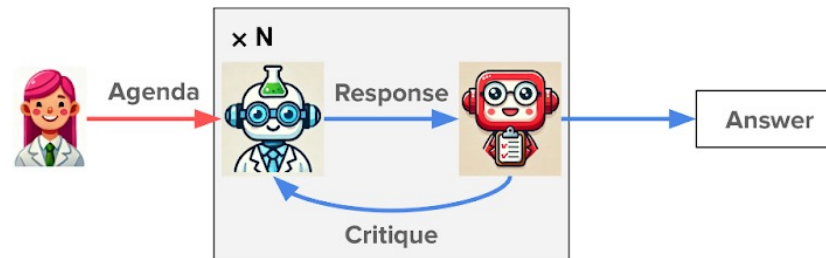
Agent creation



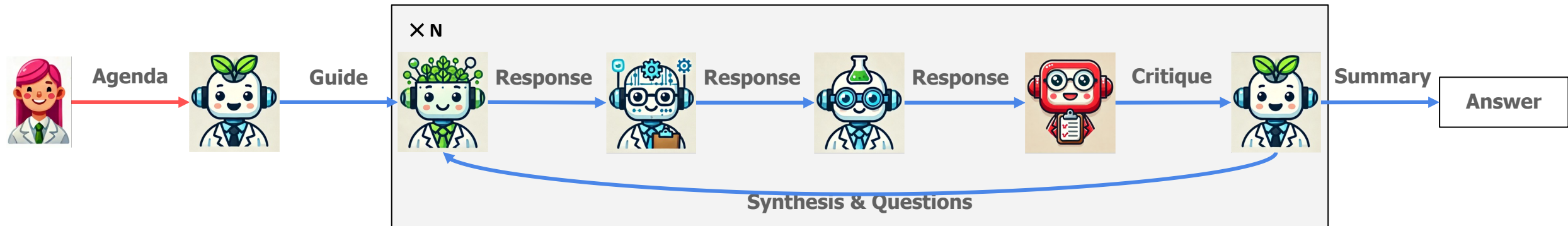
Team meeting



Individual meeting



Virtual Lab: team meeting



Discuss research directions and for all the team members to present updates.

Example Virtual Lab team meeting



Principal Investigator: I want to emphasize the significance of our objective: **to develop effective antibodies or nanobodies** that can target the newest variant of the **SARS-CoV-2 spike protein**, while also maintaining activity against other circulating minor variants and past variants.



Immunologist: I recommend **modifying existing nanobodies**. We have a wealth of data on several broadly neutralizing nanobodies that have shown efficacy against diverse SARS-CoV-2 variants. This approach **reduces the risk and time associated with de novo design**, leveraging existing structural and binding data for rapid development.



Machine Learning Specialist: I agree with the emphasis on nanobodies... Their smaller size also means fewer degrees of freedom, which can **simplify machine learning model complexity**... For modifying existing nanobodies, we can **utilize deep learning models** trained on structural and sequence data to predict changes that enhance binding affinity and cross-reactivity.

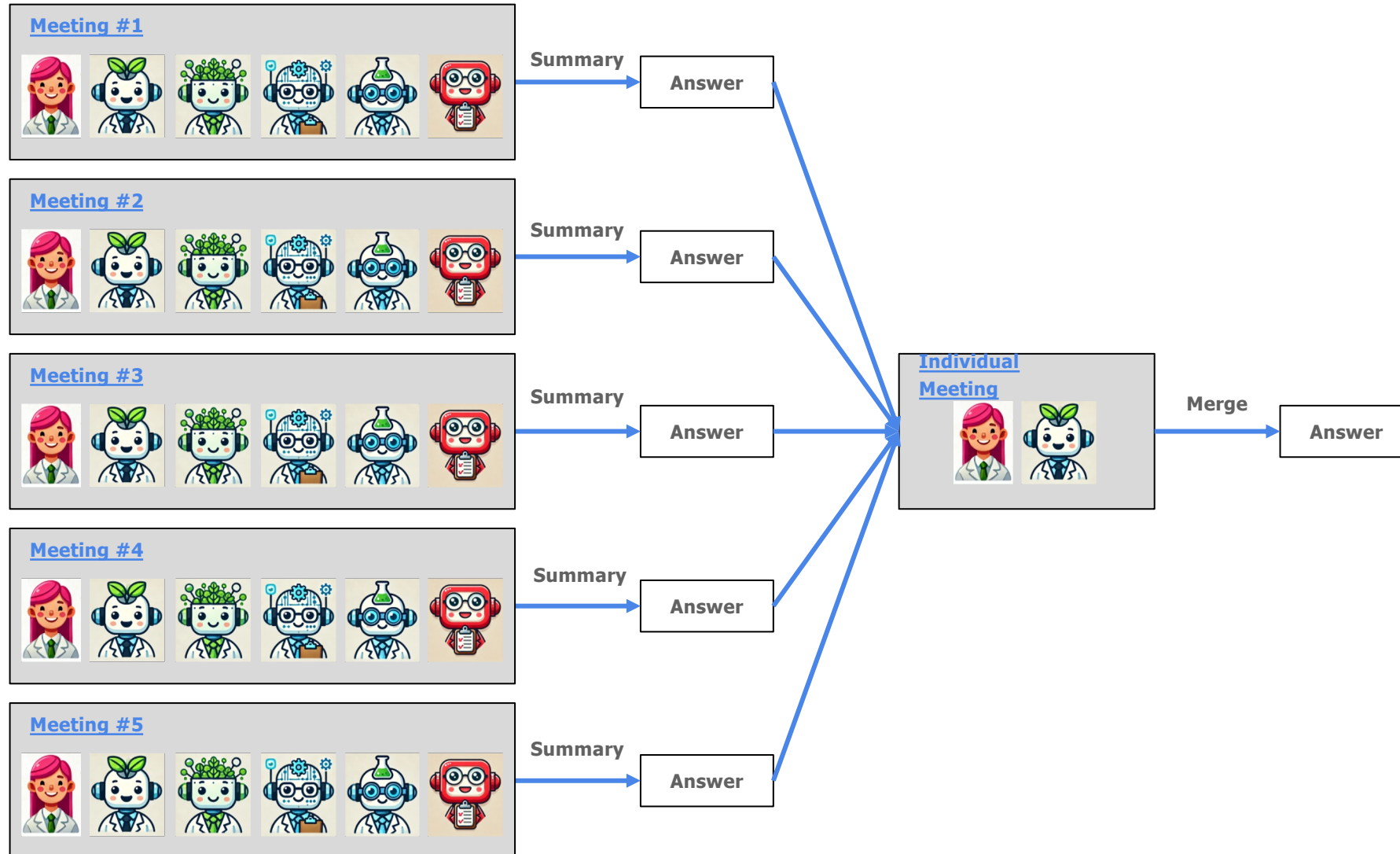


Computational Biologist: The machine learning models proposed are excellent, and coupling them with **molecular docking and simulations** can create a robust pipeline. For instance, once a machine learning model suggests modifications, simulations can be used to validate and refine these predictions by assessing the **energetic favorability and structural compatibility** with the spike protein.



Scientific Critic: We must remain **cautious of over-reliance on computational predictions** without thorough cross-validation. Machine learning models can suffer from **bias**, particularly if trained on **limited or non-representative datasets**.

Virtual Lab: parallel meetings



Words written by different agents



Princi
antibo
also m



Immu
broadl
approa
and bi



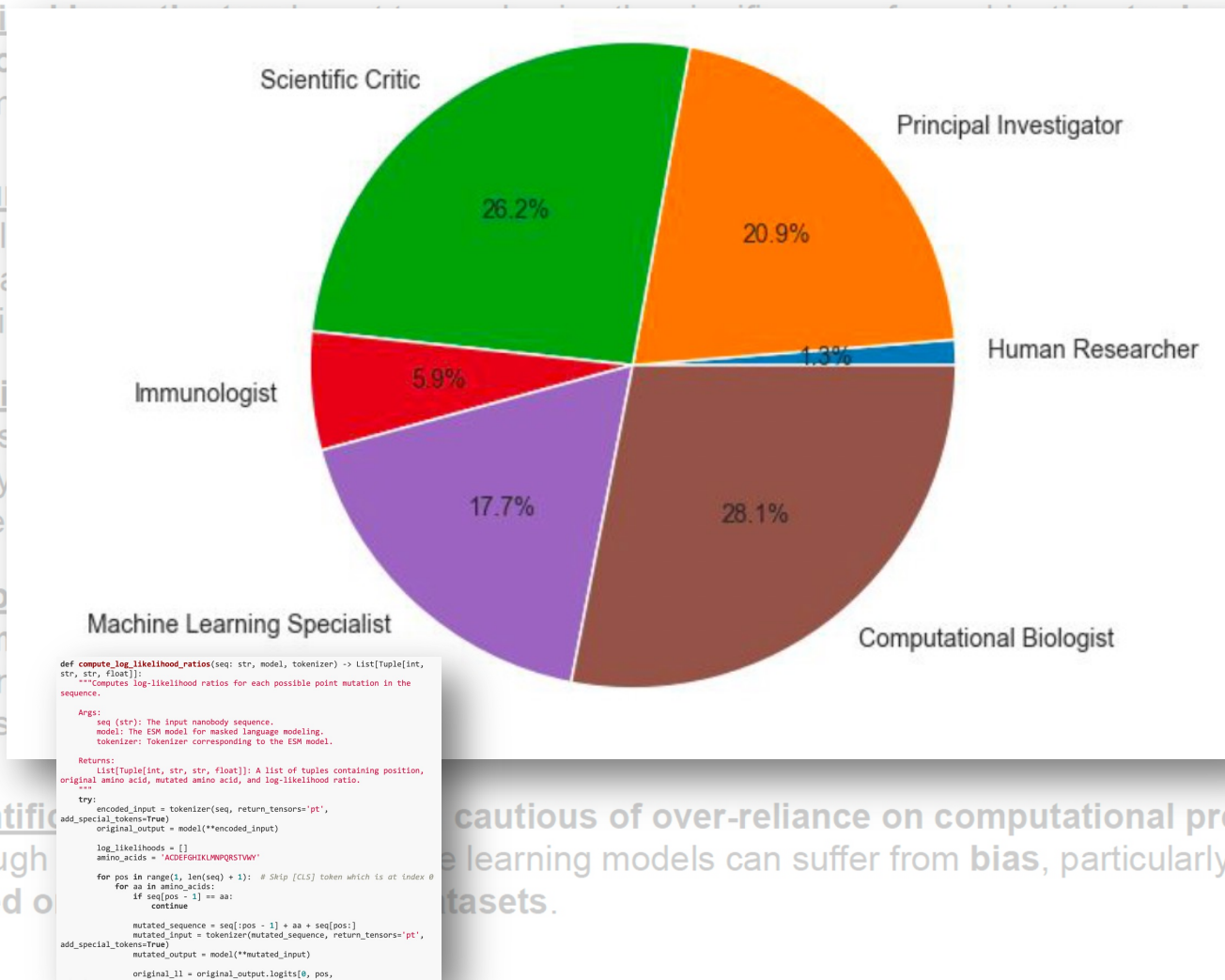
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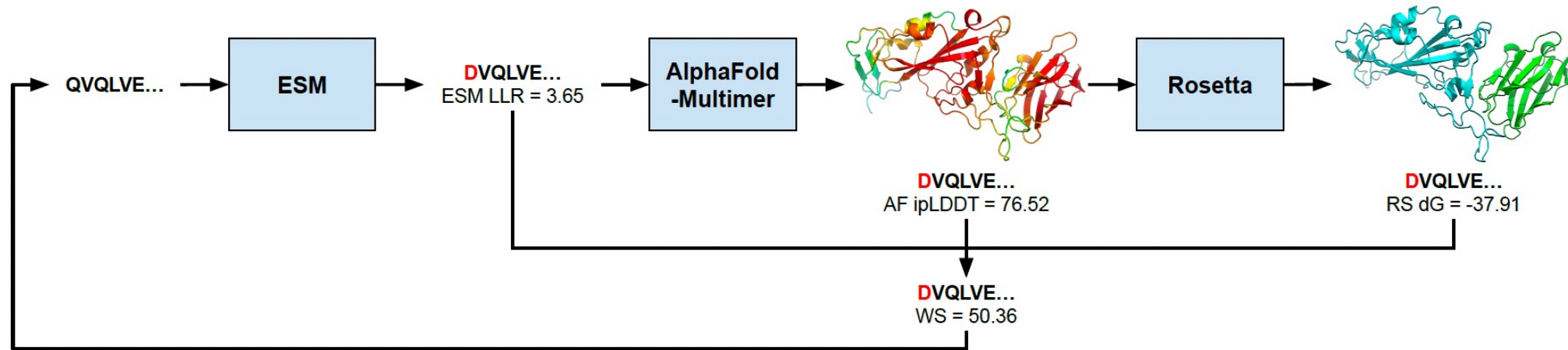
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protein.

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tatasets.

Virtual Lab designs nanobodies for recent COVID variants

Virtual lab created workflow.



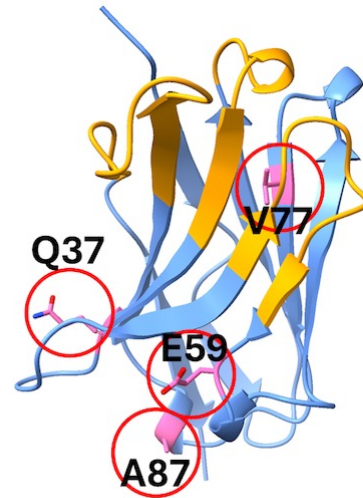
ESM2 → selected stable nanobodies

AF-Multimer → predicts nanobody + spike structure

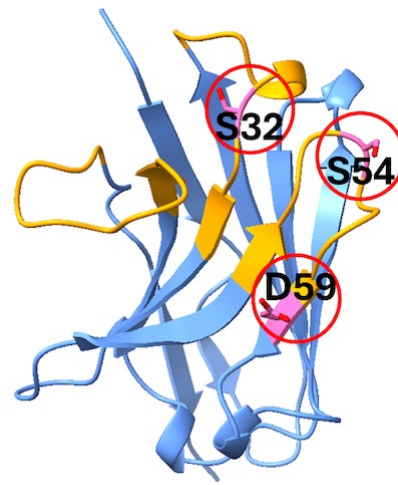
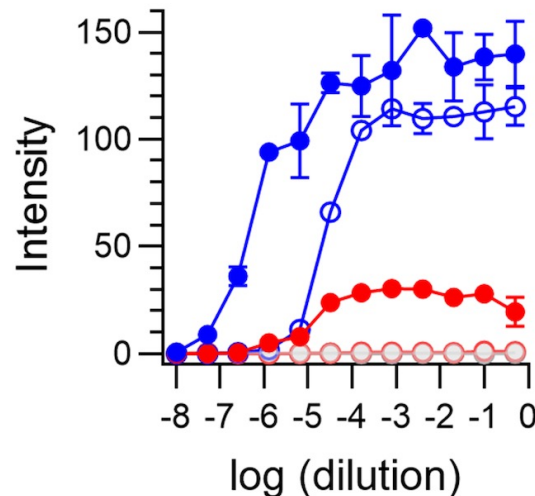
Rosetta → estimates binding energy

3 models combined to select candidates for next round.

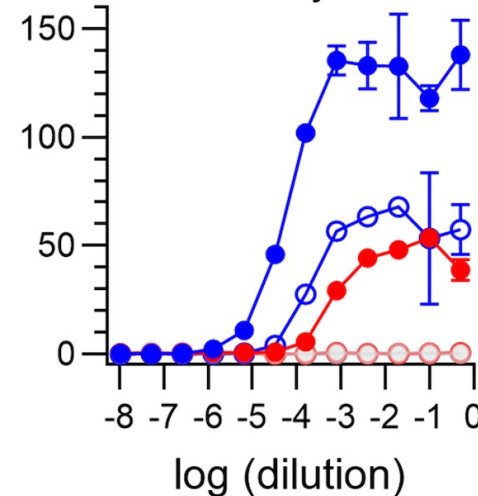
Virtual Lab designed nanobodies experimentally validated



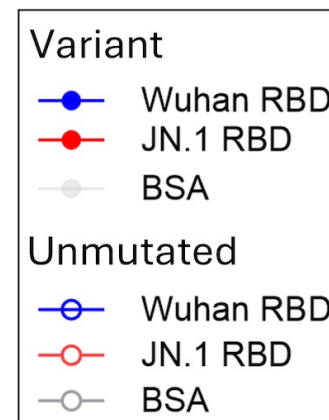
I77V-L59E-Q87A-R37Q
vs. Nb21



V32F-G59D-N54S-F32S
vs. Ty1



Promising candidates showing enhanced binding to recent JN.1 variant and the original Wuhan variant.



Virtual Lab School of self-improving AI scientists

1. Choose Topics for Agents



nanobodies

SARS-CoV-2 spike protein

SARS-CoV-2 variants KP.3 and JN.1



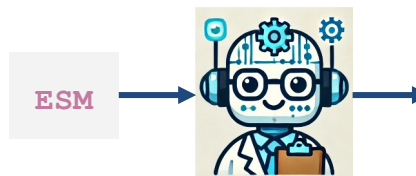
ESM



AlphaFold-Multimer

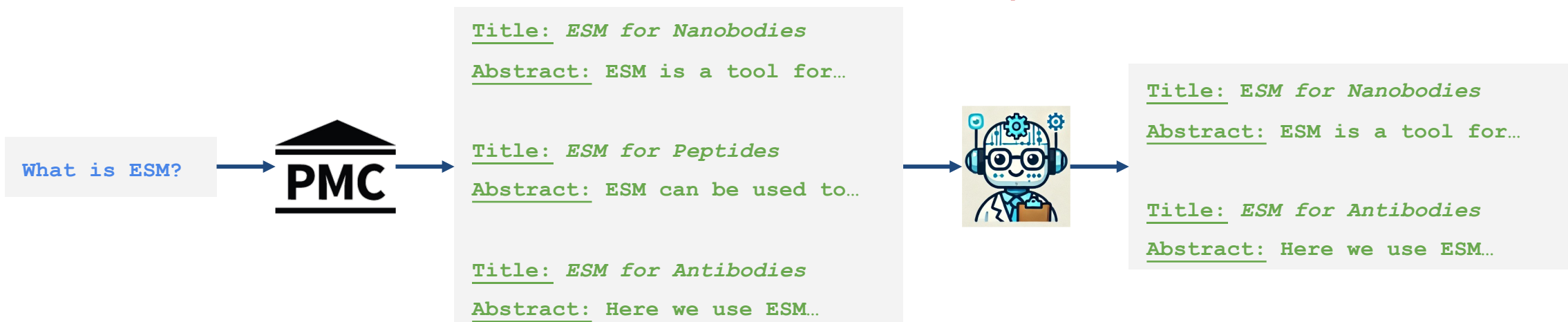
Rosetta

2. Self Generate Queries

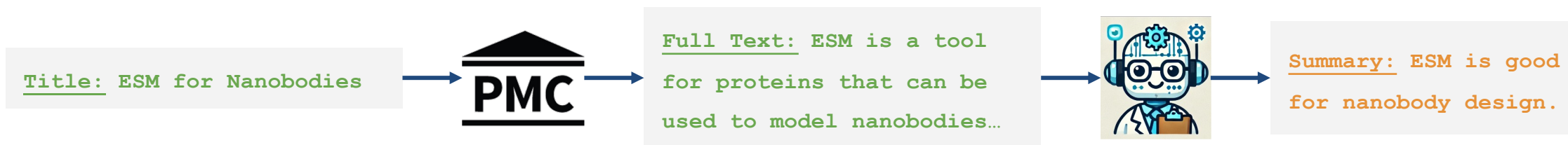


1. What is ESM?
2. How is ESM used for nanobody design?
3. How are ESM embeddings used?
4. How are ESM log-likelihoods used?
5. How to design nanobodies with ESM?

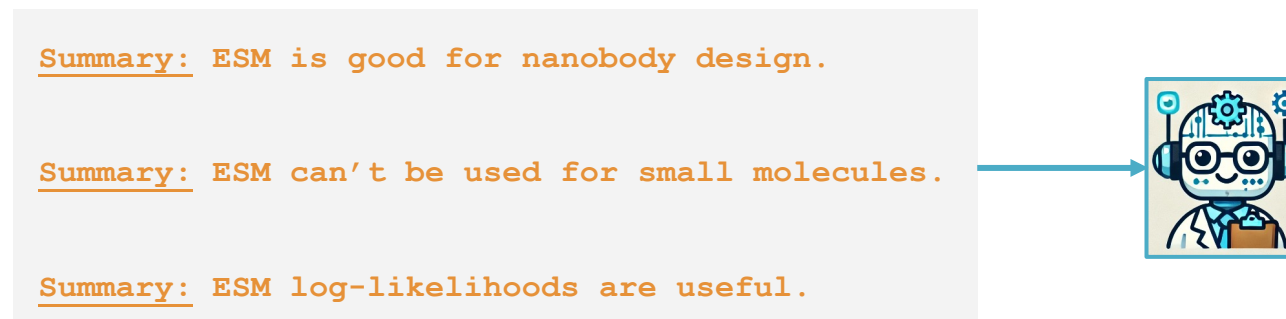
3. Search PMC & Select Papers



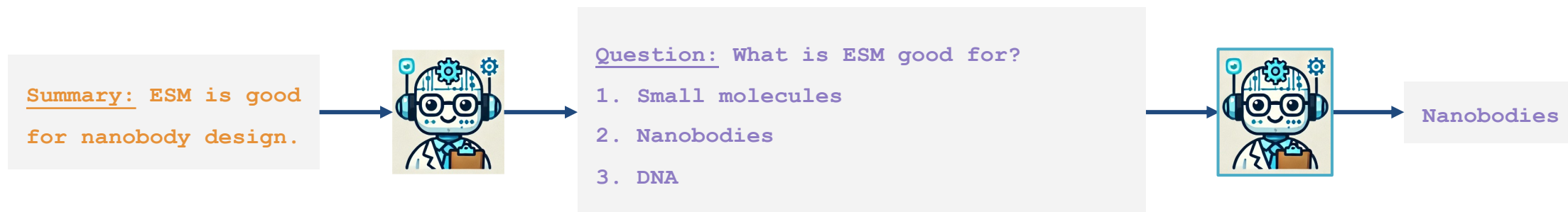
4. Summarize Papers



5. Finetune on Summaries



6. Evaluate via Q&A



AI teammates for clinical trial submissions

Obtain complete blood count on Days 1, 8, and 15 of each cycle. Assess creatinine clearance prior to each cycle. Do not administer Pemetrexed Injection if the creatinine clearance is less than 45 mL/min.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Pemetrexed Injection safely and effectively. See full prescribing information for Pemetrexed Injection.

Pemetrexed Injection, for intravenous use
Initial US Approval: 2004

INDICATIONS AND USAGE
Pemetrexed Injection is a folate analog metabolic inhibitor indicated:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. (1.1)
- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous NSCLC. (1.1)
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1)
- Limitations of Use:** Pemetrexed Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. (1.1)
- initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended dose of Pemetrexed Injection administered with pembrolizumab and platinum chemotherapy in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m² as an intravenous infusion over 10 minutes, administered after pembrolizumab and prior to platinum chemotherapy, on Day 1 of each 21-day cycle. (2.1)
- The recommended dose of Pemetrexed Injection, administered as a single agent or with cisplatin, in patients with creatinine clearance of 45 mL/minute or greater is 500 mg/m² as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. (2.1, 2.2)
- Initiate folic acid 400 mcg to 1000 mcg orally, once daily, beginning 7 days prior to the first dose of Pemetrexed Injection and continue until 21 days after the last dose of Pemetrexed Injection. (2.4)
- Administer vitamin B₁₂, 1 mg intramuscularly, 1 week prior to the first dose of Pemetrexed Injection and every 3 cycles. (2.4)
- Administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after Pemetrexed Injection administration. (2.4)

DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/10 mL, 500 mg/50 mL, 1,000 mg/100 mL in single dose vials (3)

CONTRAINDICATIONS
History of severe hypersensitivity reaction to pemetrexed. (4)

WARNINGS AND PRECAUTIONS

Myelosuppression: Can cause severe bone marrow suppression resulting in cytopenia and an increased risk of infection. Do not administer Pemetrexed Injection when the absolute neutrophil count is less than 1500 cells/mm³ and platelets are less than 100,000 cells/mm³. Initiate supplementation with oral folic acid and intramuscular vitamin B₁₂ to reduce the severity of hematologic and gastrointestinal toxicity of Pemetrexed Injection. (2.4, 5.1)

Renal Failure: Can cause severe, and sometimes fatal, renal failure. Do not administer when creatinine clearance is less than 45 mL/min. (2.3, 5.2)

Bullous and Exfoliative Skin Toxicity: Permanently discontinue for severe and life-threatening bullous, blistering or exfoliating skin toxicity. (5.3)

Interstitial Pneumonitis: Withhold for acute onset of new or progressive unexplained pulmonary symptoms. Permanently discontinue if pneumonitis is confirmed. (5.4)

Radiation Recall: Can occur in patients who received radiation weeks to years previously; permanently discontinue for signs of radiation recall. (5.5)

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

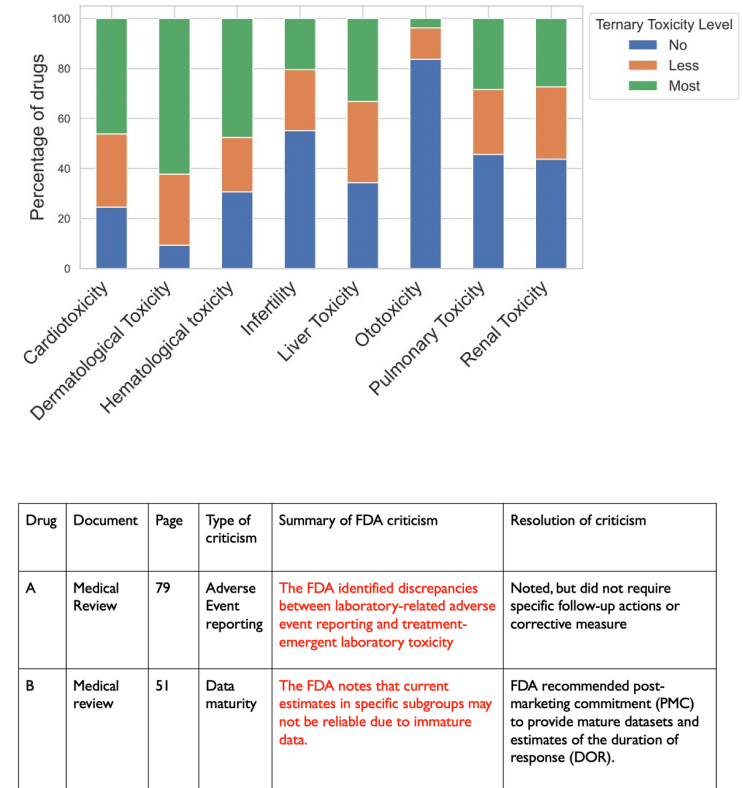
- The most common adverse reactions (incidence ≥20%) of pemetrexed injection, when administered as a single agent are fatigue, nausea, and anorexia. (6.1)
- The most common adverse reactions (incidence ≥20%) of pemetrexed injection when administered with cisplatin are vomiting, neutropenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)
- The most common adverse reactions (incidence ≥20%) of pemetrexed injection when administered in combination with pembrolizumab and platinum chemotherapy are fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, and pyrexia. (6.1)

DRUG INTERACTIONS
Ibuprofen increased risk of Pemetrexed Injection toxicity in patients with mild to moderate renal impairment. Modify the ibuprofen dosage as recommended for patients with a creatinine clearance between 45 mL/min and 79 mL/min. (2.5, 5.6, 7)

USE IN SPECIFIC POPULATIONS
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised:05/2023



FDA labels
>100K pages of PDFs

Virtual Lab: broad roster of AI scientists with deep expertise

AI chemist



AI data scientist



AI pathologist



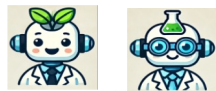
AI immunologist



AI tox specialist



...and more!



Drug discovery work



Preclinical laboratory, in-vitro, ex-vivo, and in-vivo research



First-in-human and phase 1 trials



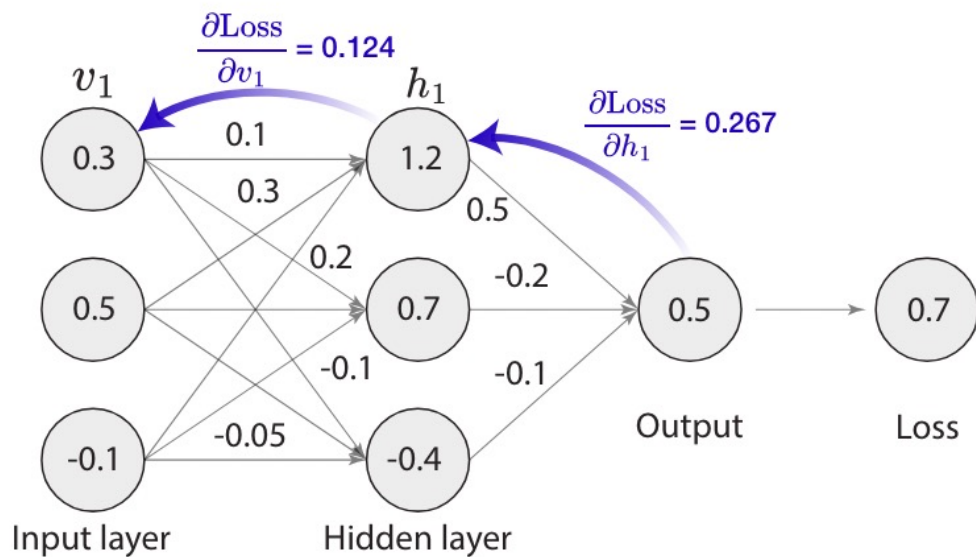
Phase 2 and phase 3 clinical trials



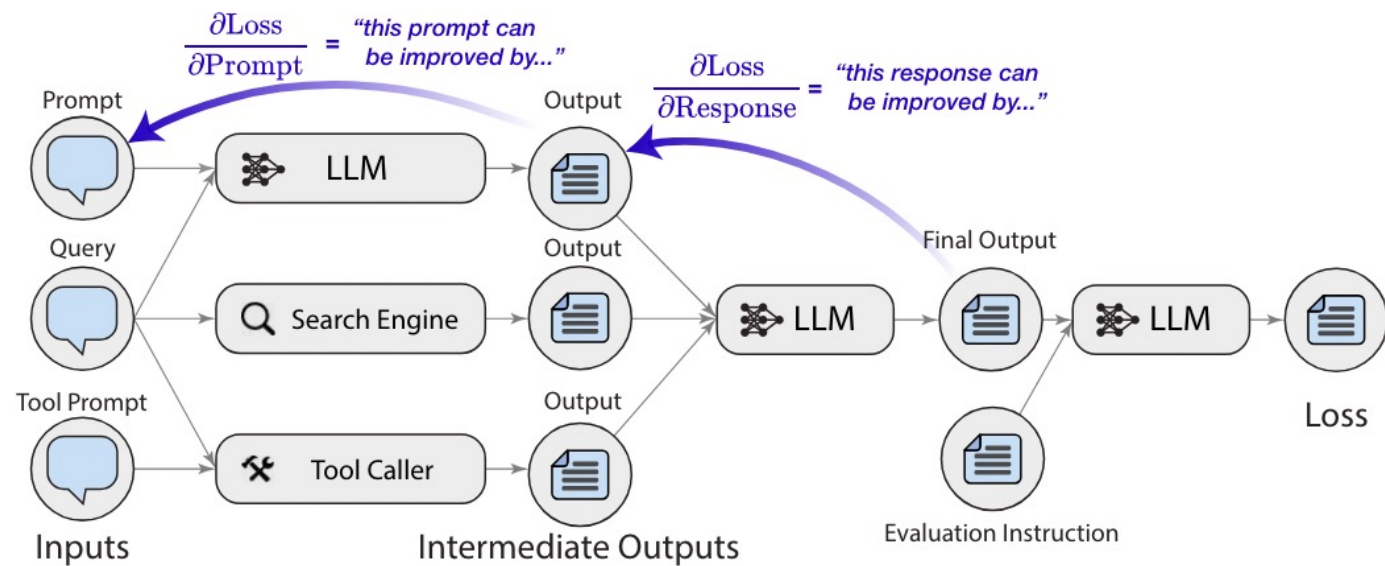
Regulatory approval and clinical use

TextGrad: autograd for AI agents

Standard deep learning:
backprop gradients

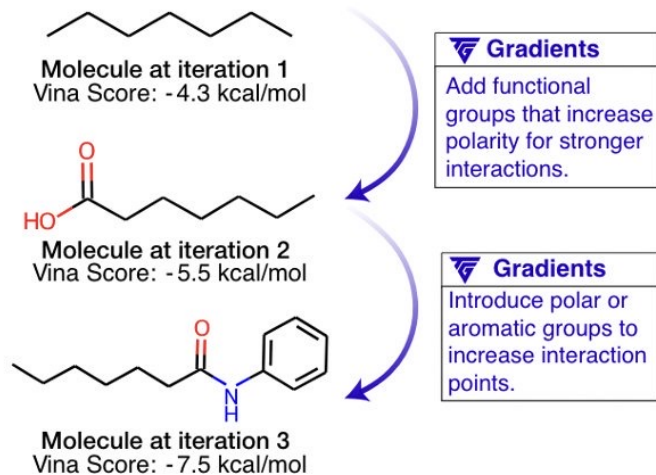


Systems of agents:
backprop text feedback



TextGrad: flexible optimization of AI agents

TextGrad for molecule optimization



TextGrad for code optimization

```
for i in range(n):  
    if nums[i] < k:  
        balance -= 1  
    elif nums[i] > k:  
        balance += 1  
    if nums[i] == k:  
        result += count.get(balance, 0) +  
            count.get(balance - 1, 0)  
    else:  
        result += count.get(balance, 0)  
        count[balance] = count.get(balance, 0) + 1
```

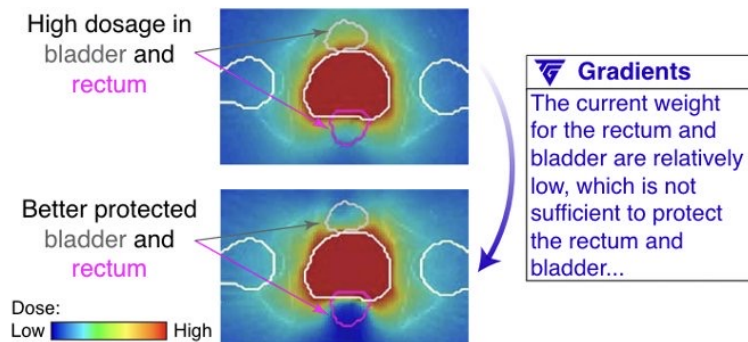
Code at iteration t

```
for i in range(n):  
    if nums[i] < k:  
        balance -= 1  
    elif nums[i] > k:  
        balance += 1  
    else:  
        found_k = True  
    if nums[i] == k:  
        result += count.get(balance, 0) +  
            count.get(balance - 1, 0)  
    else:  
        count[balance] = count.get(balance, 0) + 1
```

Code at iteration t+1

Gradients
**Handling `nums[i] == k`: The current logic does not correctly handle the case when `nums[i] == k`. The balance should be reset or adjusted differently when `k` is encountered. ...

TextGrad for treatment plan optimization



TextGrad for prompt optimization

You will answer a reasoning question. Think step by step. The last line of your response should be of the following format: 'Answer: \$VALUE' where VALUE is a numerical value.

Prompt at initialization (Accuracy = 77.8%)

You will answer a reasoning question. List each item and its quantity in a clear and consistent format, such as '- Item: Quantity'. Sum the values directly from the list and provide a concise summation. Ensure the final answer is clearly indicated in the format: 'Answer: \$VALUE' where VALUE is a numerical value. Verify the relevance of each item to the context of the query and handle potential errors or ambiguities in the input. Double-check the final count to ensure accuracy."

Prompt after optimization (Accuracy = 91.9%)

TextGrad improves LLM performance on:

1. LeetCodeHard
2. Google-proof QA
3. Treatment planning
4. Molecule opt.

TextGrad: Automatic “Differentiation” via Text



Chain rule for text

TextGrad: Automatic “Differentiation” via Text



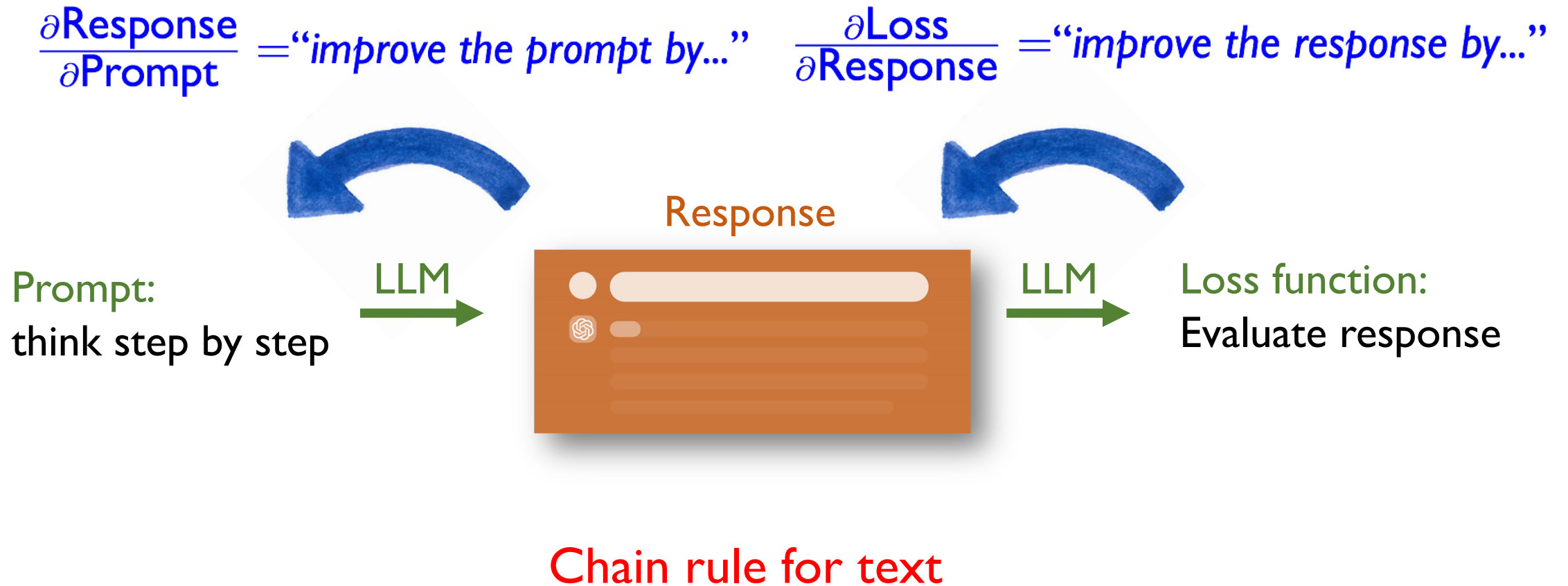
Chain rule for text

TextGrad: Automatic “Differentiation” via Text



Chain rule for text

TextGrad: Automatic “Differentiation” via Text





TextGrad: Automatic “Differentiation” via Text



Chain rule for text

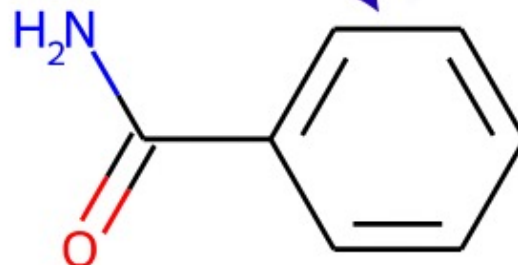
TextGrad designs new druglike molecules

 **Gradients:** Introduce functional groups that can form hydrogen bonds or hydrophobic interactions.

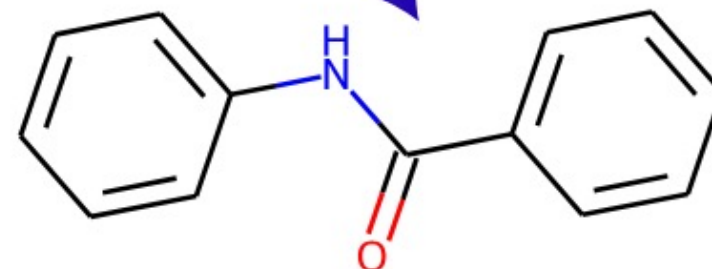
 **Gradients:** Add hydrophobic groups or aromatic rings to enhance interactions ... while maintaining a balance of hydrophobic and hydrophilic properties.



Vina: -4.2 kcal/mol
QED: 0.44



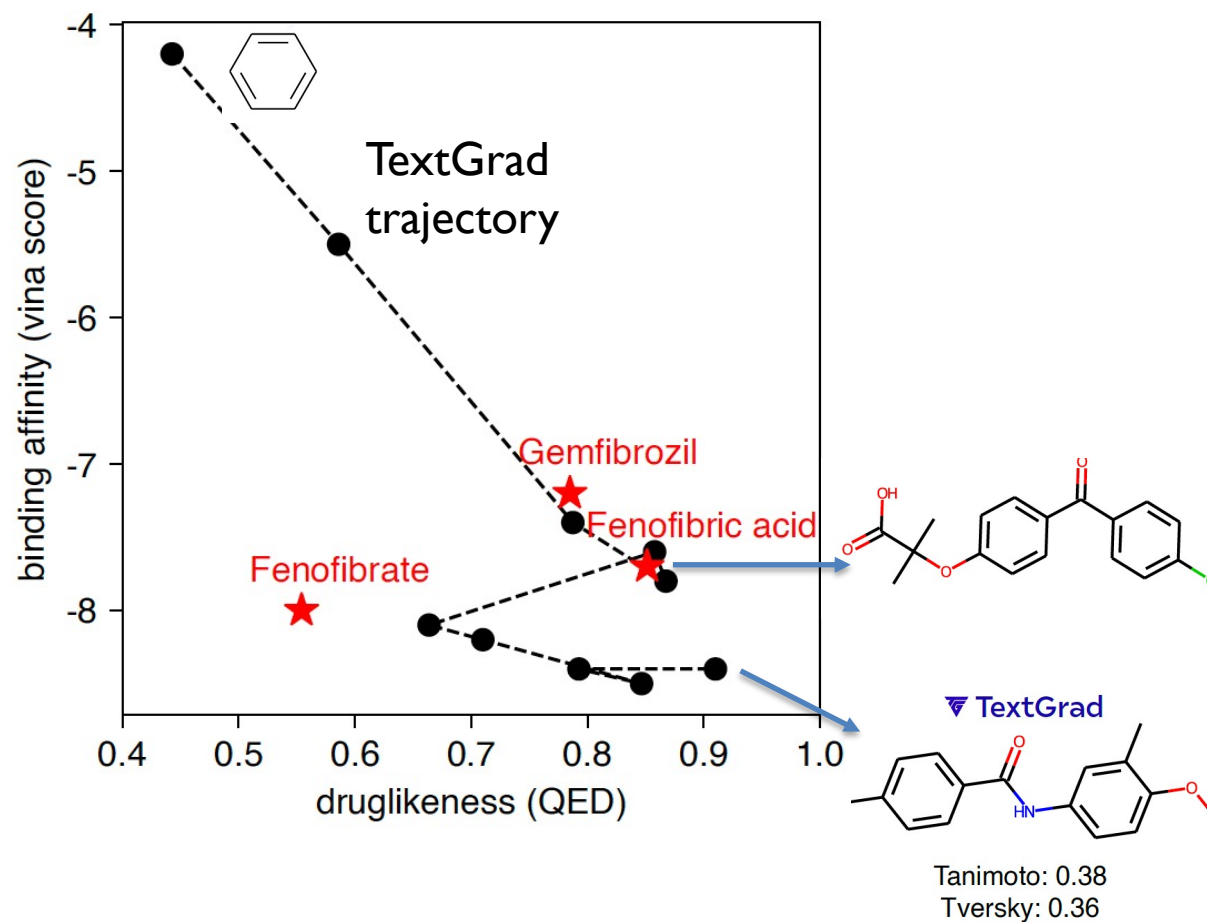
Vina: -5.5 kcal/mol
QED: 0.59



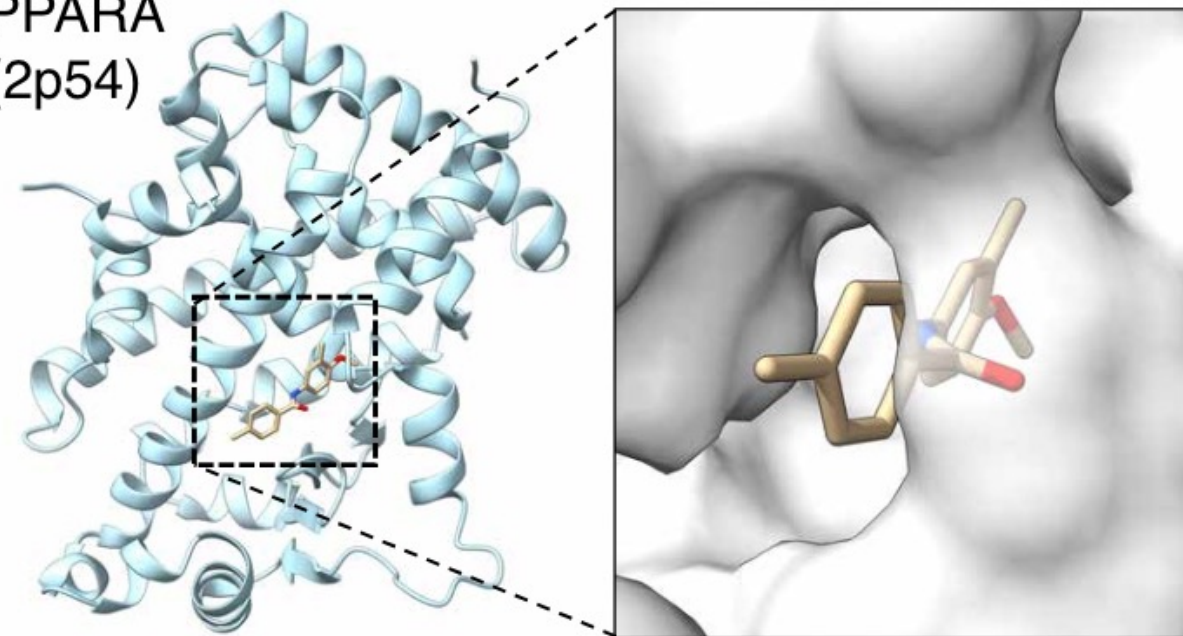
Vina: -7.5 kcal/mol
QED: 0.79

Molecule optimization

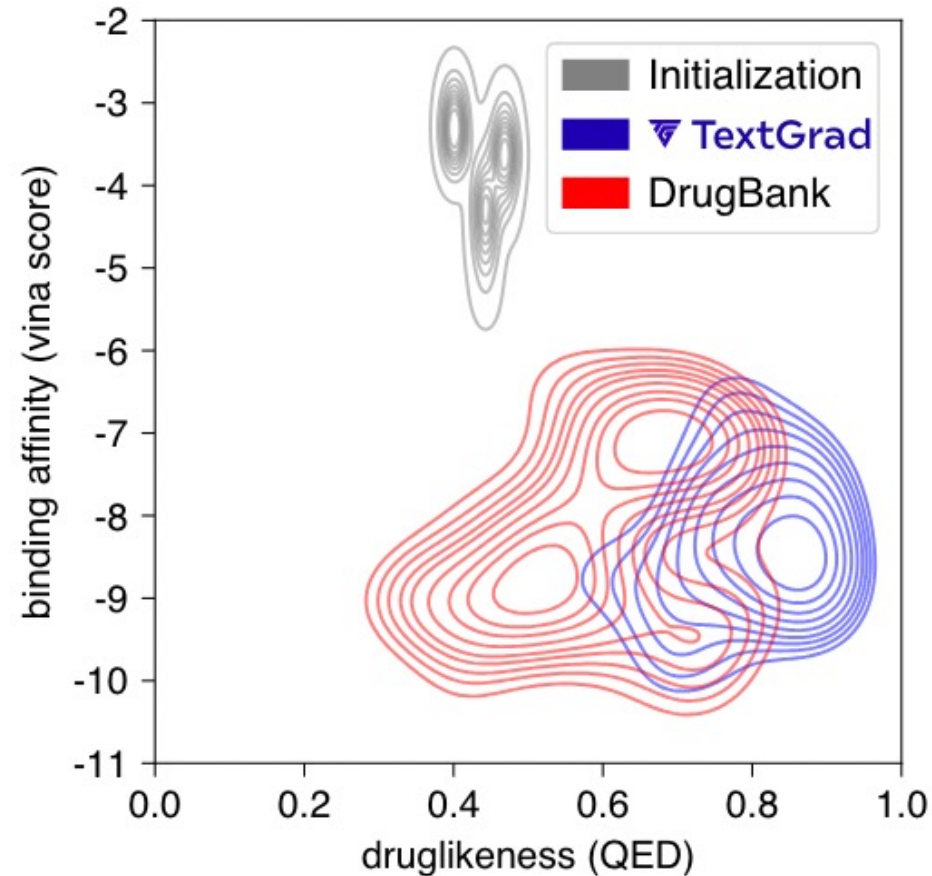
TextGrad optimizes desirable molecular properties



PPARA
(2p54)



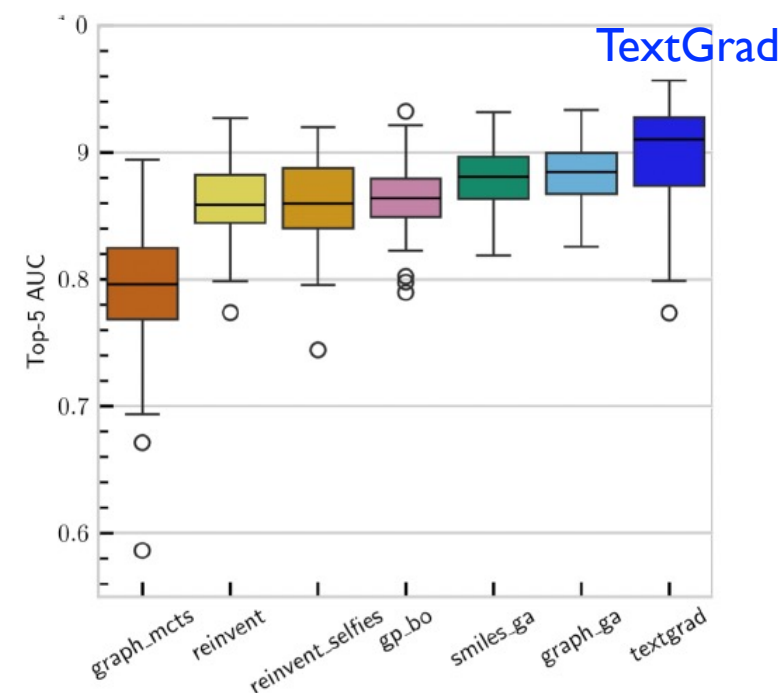
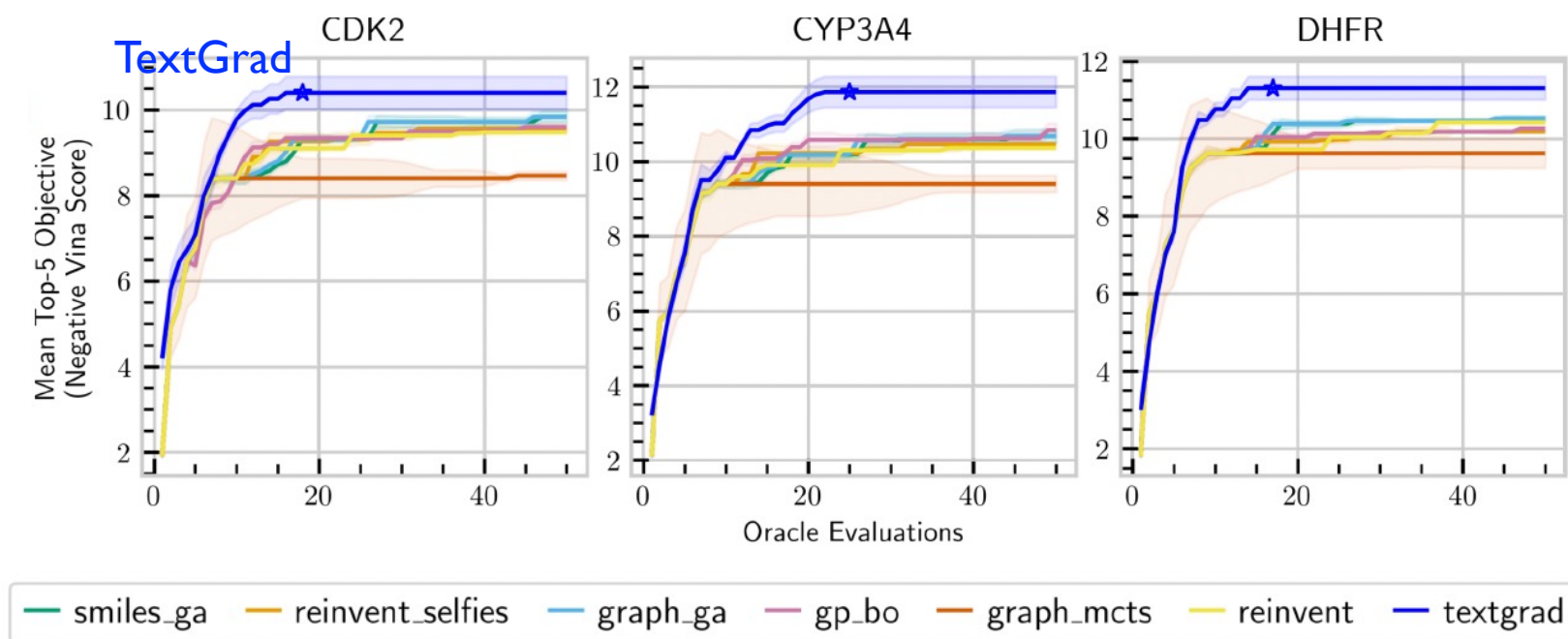
TextGrad designs desirable and novel small molecules



Optimizing binders to 58 target proteins

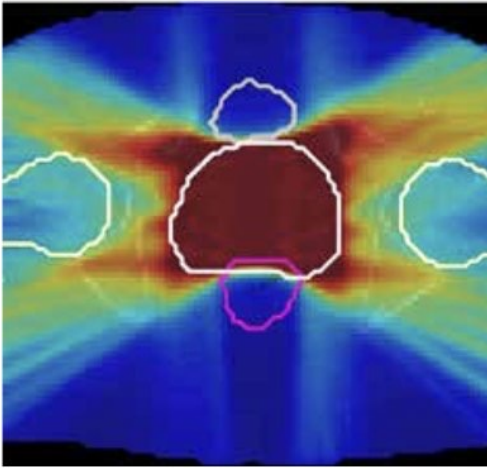
TextGrad improves over previous molecule optimizers

Target protein




TextGrad improve radiation oncology treatment planning

Initialization



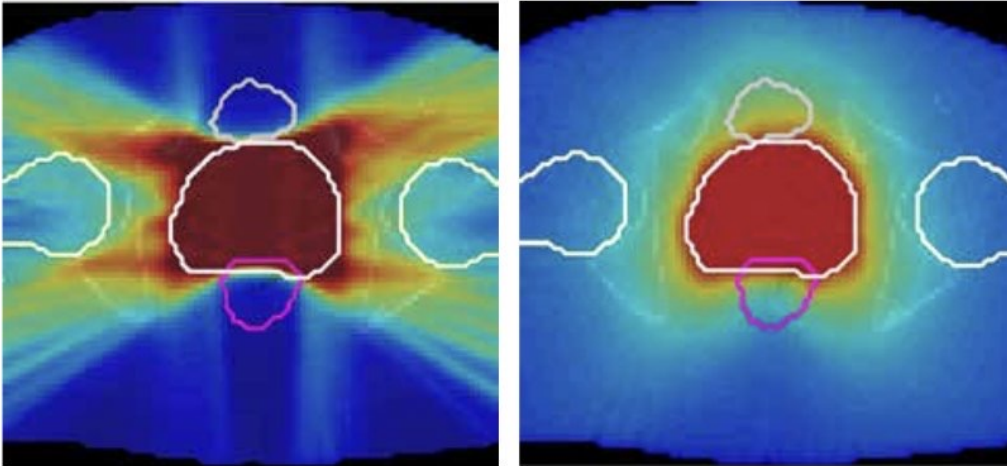
Goal: increase radiation in target region while minimizing radiation outside

TextGrad improve radiation oncology treatment planning

 **Gradients:** The current plan does not meet the criteria for the PTV. The constraints on OARs are currently being met Recommendation: Increase the importance weight for the PTV.

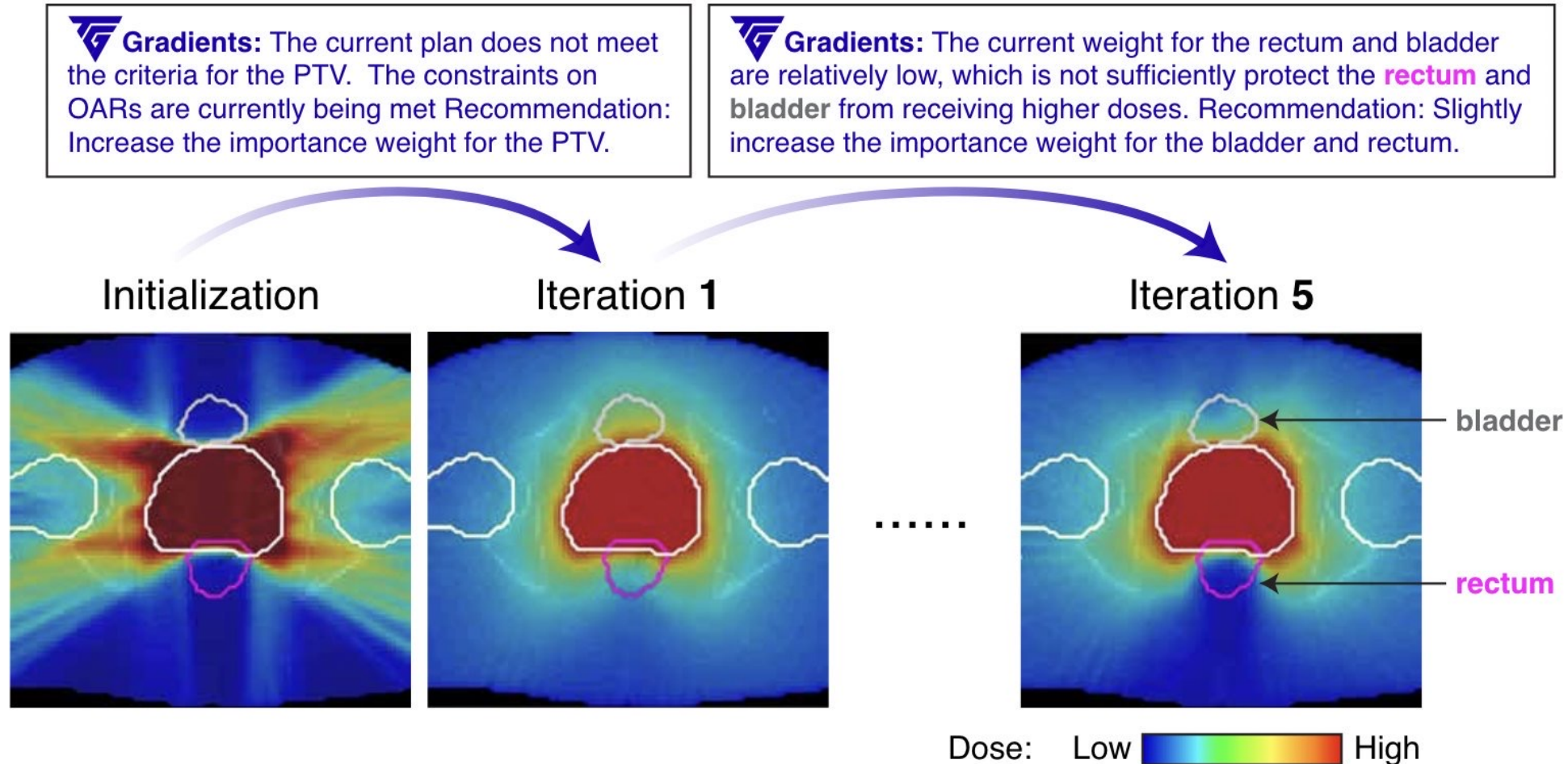
Initialization

Iteration 1




Goal: increase radiation in target region while minimizing radiation outside


TextGrad improve radiation oncology treatment planning



Goal: increase radiation in target region while minimizing radiation outside

TextGrad improve radiation oncology treatment planning

 Gradients
the criteria for
OARs are curr
Increase the in

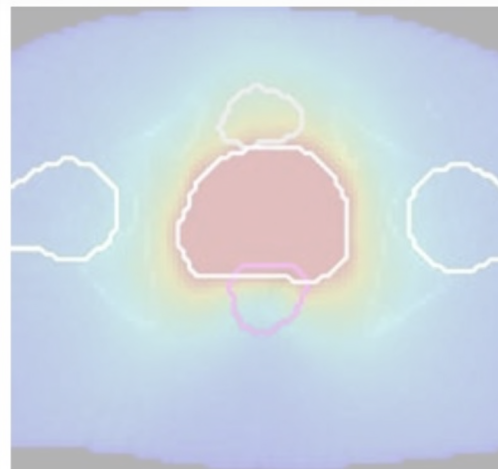
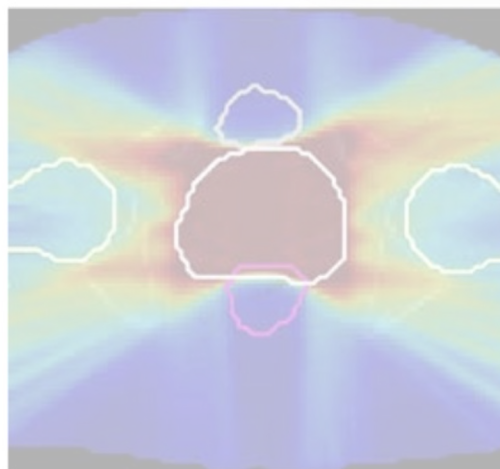
Target	Method	Mean dose [Gy]	D ₉₅ [Gy]
PTV	Clinical Goal	70.20	70.20
	Radiation Oncologist	+1.97 (0.36)	-0.10 (0.15)
	 TextGrad	+0.51 (0.09)	+0.00 (0.00)

m and bladder
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ondation: Slightly
and rectum.

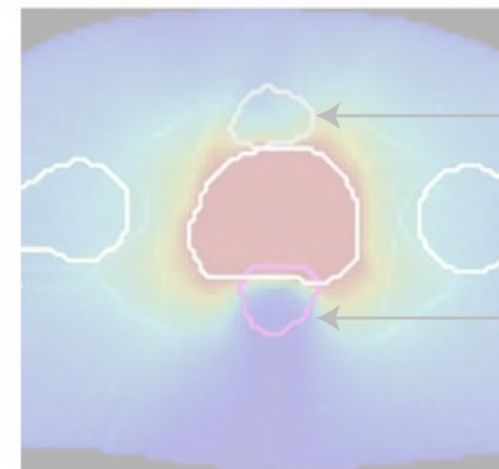
Initialization

Iteration 1

Iteration 5



.....



bladder

rectum

Dose: Low  High