

# AI - Medicine

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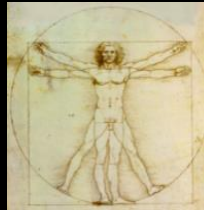
# Medicine is a Science of Uncertainty and an Art of Probability

Sir William Osler, 1849 – 1919

- Father of Modern Medicine
- One of four founding physicians of Johns Hopkins Hospital

## Three Unanswered Questions - Since the Beginning of Medicine

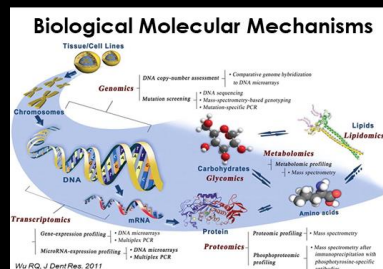
Drug/Dose



Efficacy / Toxicity

Can not predict the efficacy/Toxicity.

Quantitative Governing Rule?



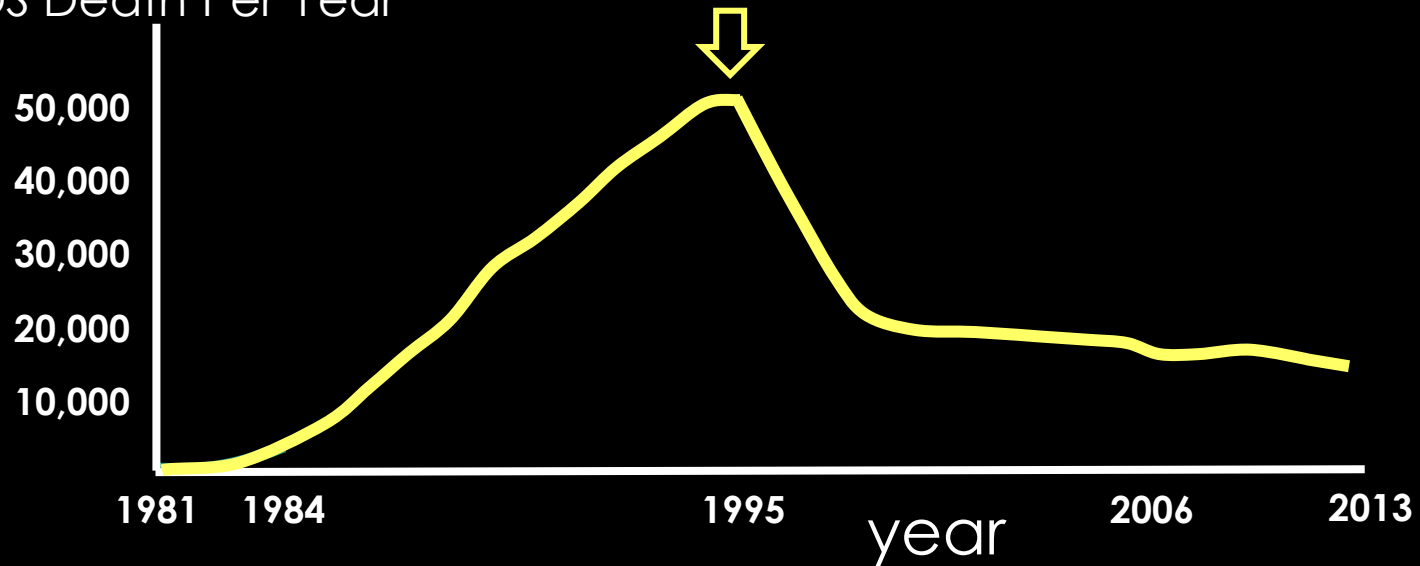
There must be a system governing rule

言天下之至動而不可亂也

易经繫詞

# Almost All Diseases Treated by Combinatorial Drug

AIDS Death Per Year



- All combinatorial drugs are **NOT** optimized
- N dosing levels each for M drugs:  $N^M$  combinations ( $10^6 = 1,000,000$ )

How can we identify the **optimal** drug-dose combination from such a large search space?

# Medicine is a Science of Uncertainty and an Art of Probability

Sir William Osler, 1849 – 1919

100 years later

- Sir Osler's statement **still remains to be true.**
- Despite large human diversities, **population-averaged regimen** for all patients of same disease - 同病同药
- Population-averaged Chemotherapy, **1 out 4 patients** has response

Population  
averaged  
Chemotherapy

Cancer Type	Response Rate	Median Survival
Breast	25-55%	24-36 months
Colon	25-35%	12-18 months
Stomach	20-30%	6-9 months
Pancreas	15-25%	6-9 months
Liver (Hepatoma)	5-15%	6-9 months

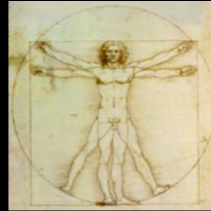
DeVita, Hellman, and Rosenberg.  
Cancer: Principles and Practice of Oncology

Personalized Therapy - 依人使药 ?

# Artificial Intelligence (AI)

Bridging inputs and outputs with a quantitative relation

Drug  
&  
Dose



Efficacy

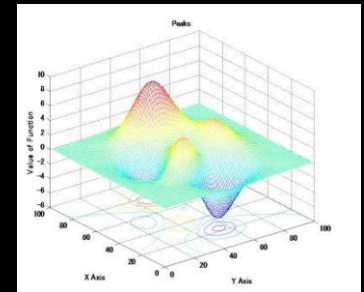
- A smart surface fitting methodology

Training Data



AI Algorithm

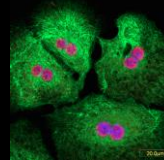
Find the landscape



- AI bypasses the mechanism-based approaches and is a **mechanism-free method**
- **Indication agnostic**: Applicable to all diseases

# AI (Neural Networks) enabled combinatorial regimen optimization

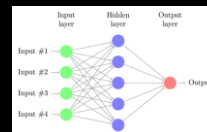
Ribavirin, Acyclovir, TNF- $\alpha$   
IFN  $\alpha$ , IFN  $\beta$ , IFN  $\gamma$   
10 dosing levels for each drug  
– 1,000,000 combinations



HSV-1  
Infection rate

## Neural Networks

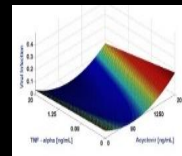
Training Data



Drug-Dose  
Response Surface

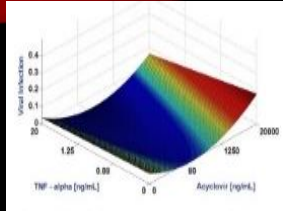
## Phenotypic Response Surface (PRS)

Drug / Dose



Efficacy / Toxicity

# Discovery



## AI - PRS Equation

$$E(C, t) = x_0 + \sum_{i=1}^M x_i c_i + \sum_{i=1}^M y_{ii} c_i^2 + \sum_{i=1}^{M-1} \sum_{j=i+1}^M z_{ij} c_i c_j$$

$C_i$  : dose

Drug-Drug Interactions

PRS is a parabolic surface

Two Drugs:

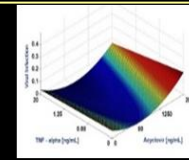
$$E(C, t) = x_0 + x_1 c_1 + x_2 c_2 + y_{11} c_1^2 + y_{22} c_2^2 + z_{12} c_1 c_2$$

## Quantitative Governing Rule

Drug / Dose

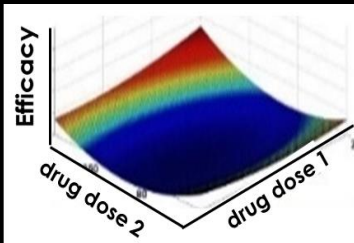


$$E(C, t) = x_0 + \sum_{i=1}^N x_i c_i + \sum_{i=1}^N y_{ii} c_i^2 + \sum_{i=1}^{N-1} \sum_{j=i+1}^N z_{ij} c_i c_j$$



Efficacy / Toxicity

## Small Data AI Enables AI - Medicine



M drug calibration tests

3	10
4	15
12	91
44	990

Search space  $N^M$  ( $N=10$ )

1,000
10,000
$10^{12}$
$10^{44}$

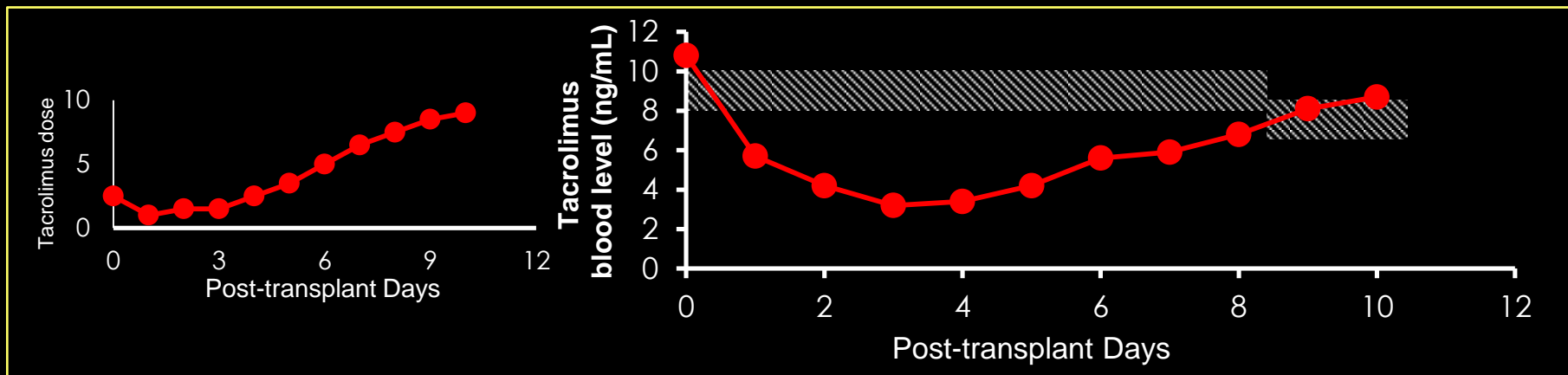
Make Personalized Medicine Possible



# Phenotypic Personalized Medicine (PPM)

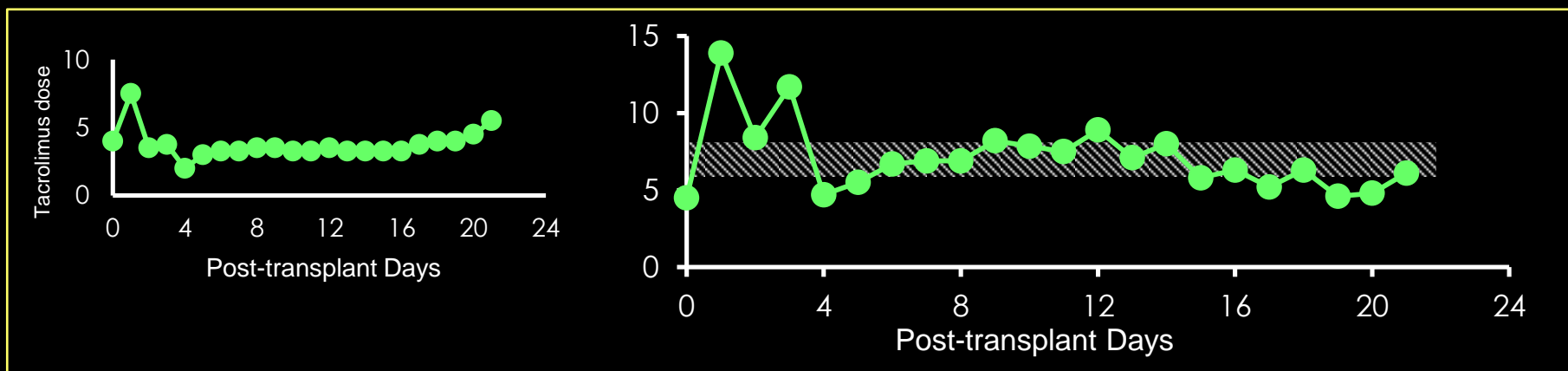
## Immunosuppression Post Liver Transplant

### Control Patient



### Prospective Test

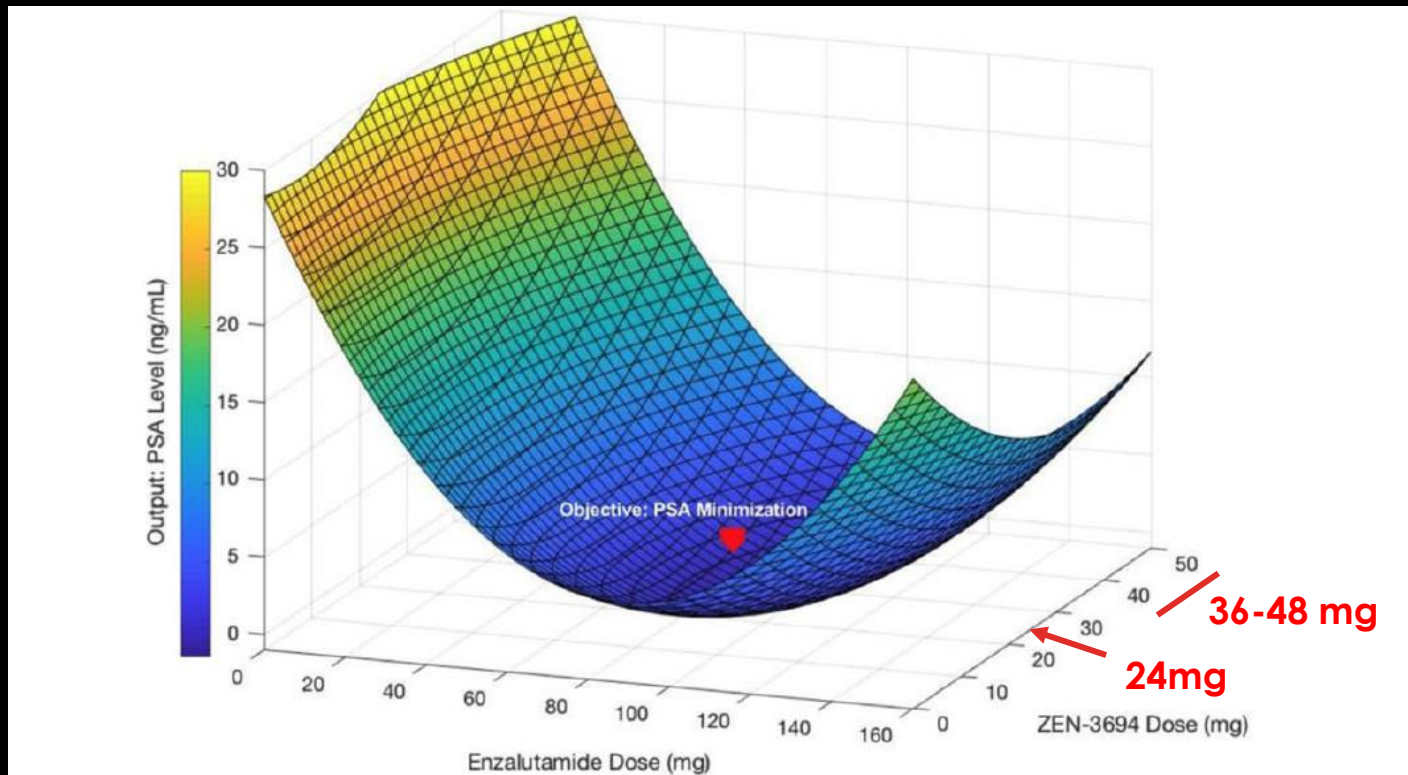
### PPM Patient





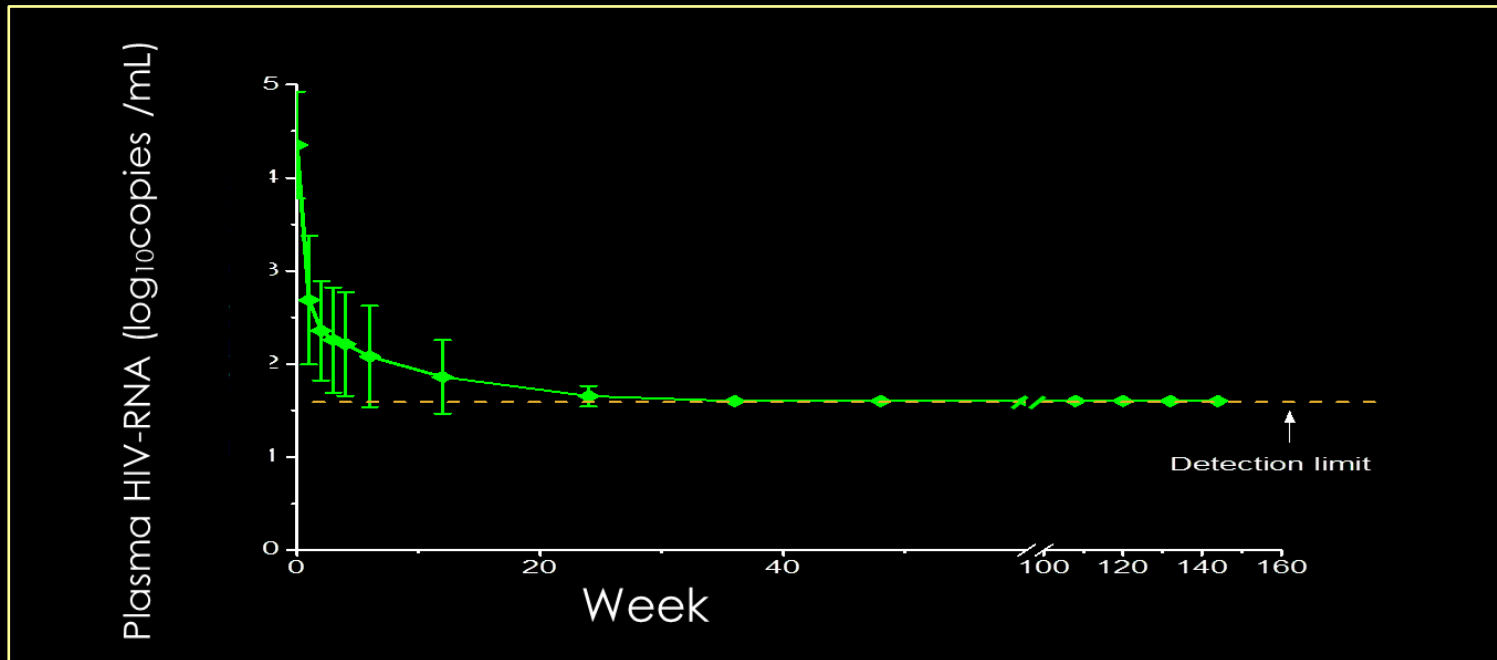
# AI-PRS Guided Personalized Dosing in a Metastatic Prostate Cancer Patient

- 85 years old patient with metastatic prostate cancer
- Regimen: BET Bromodomain Inhibitor ZEN – 3694  
Enzalutamide
- PSA: 30 - 0.64



# Maintenance Regimen for HIV Patients

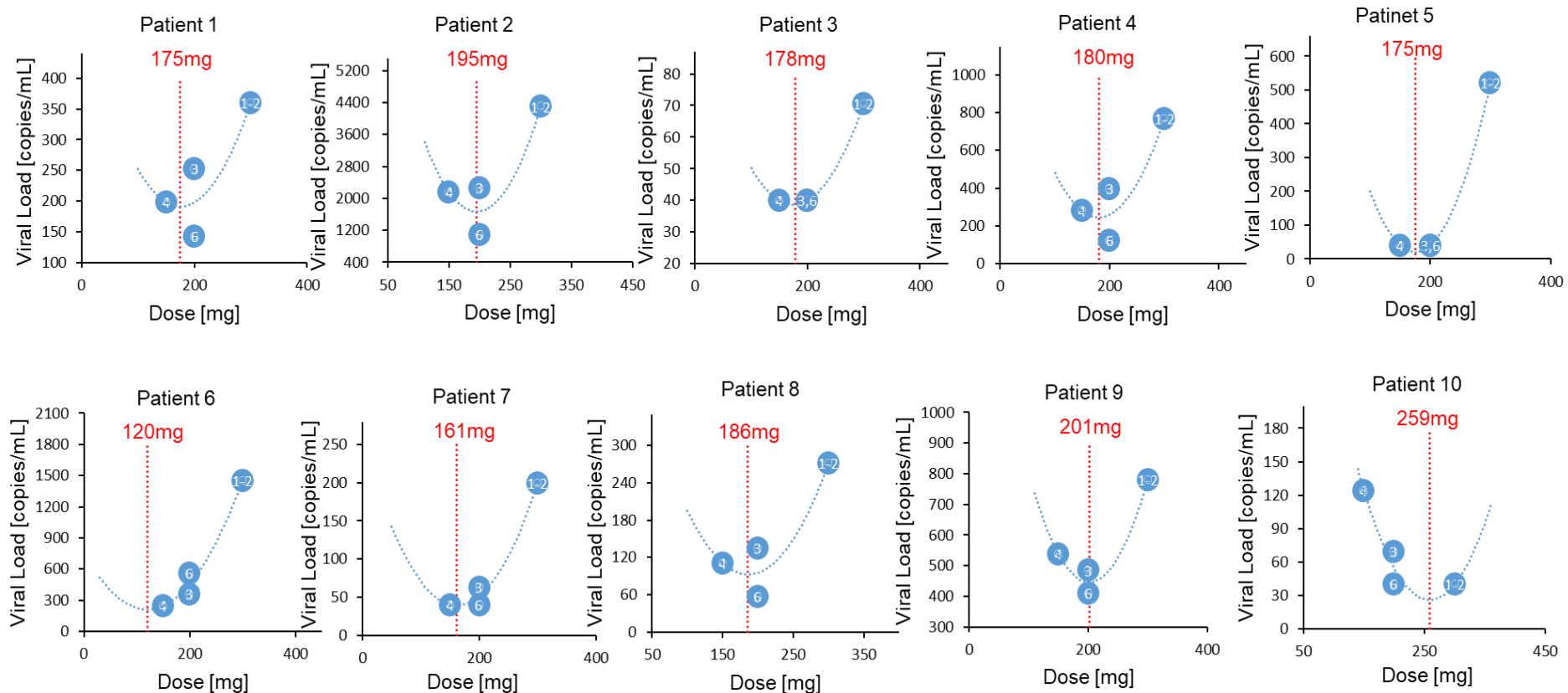
Regimen: 3TC-300mg / EFV-400mg / TDF- 300mg



Long term side effects TDF: kidney failure, osteoporosis and . . .

Maintenance Regimen: 3TC-300mg / EFV-400mg / TDF- ???mg

# AI-PRS Based Personalized Maintenance Dose for HIV Patient



- Personalized TDF maintenance dose: 120 mg – 259 mg
- All patients have been follow for 3 years, no relapse

# AI - PRS Platform

- Mechanism Free and Indication Agnostic -

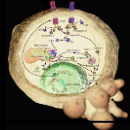
## Infectious Diseases



HSV -1  
KSHV  
VSV  
HIV  
TB

COVID-19

## Cancers



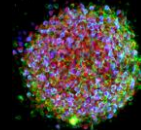
Lung cancer  
Colon cancer  
Liver cancer  
Bladder cancer  
Multiple Myeloma  
Breast cancer  
Renal cancer  
Pediatric ALL  
Prostate Cancer  
B Cell Lymphoma

## Organ Transplant



Kidney  
Liver  
Heart

## Regenerative Medicine



hES cell  
mES cell  
Bone  
regeneration

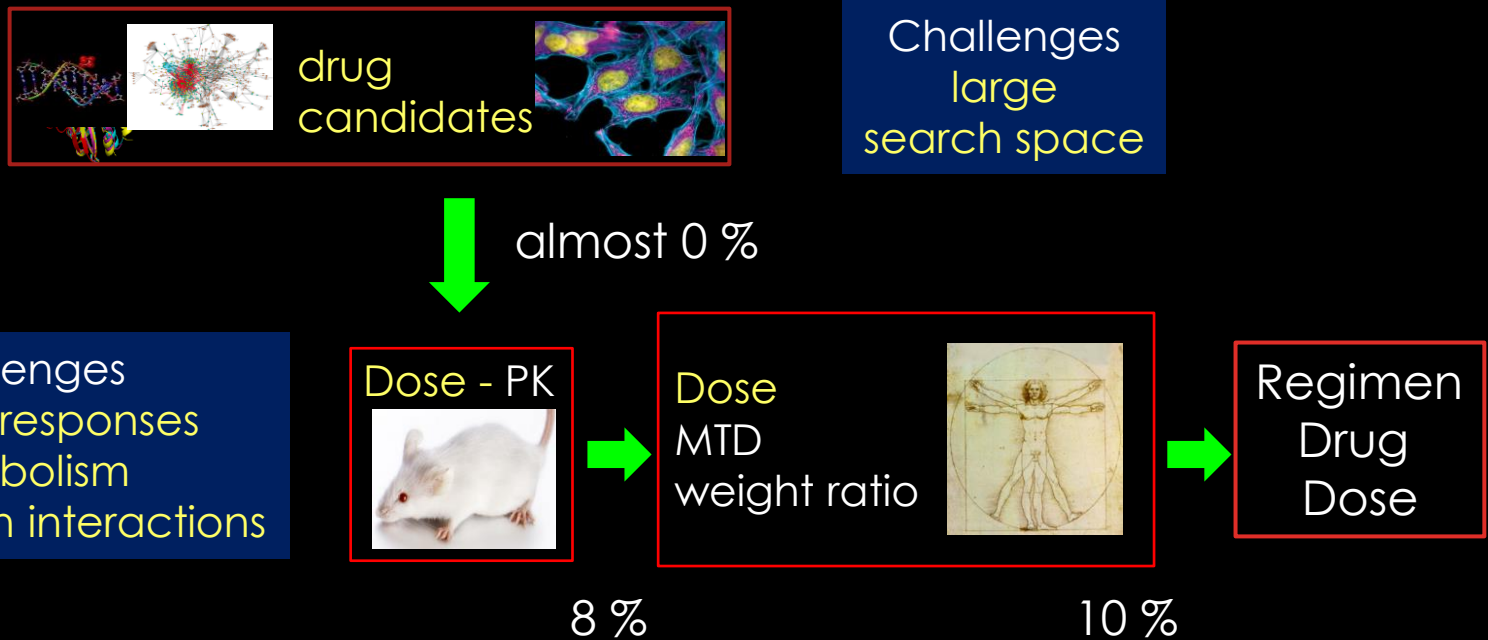
## Bio-systems



Chinese Medicine  
Parasite control  
Aptamer folding

- past 5 years - 4 pilot clinical trials (> 150 patients) - 0 misses
- 7 ongoing clinical trials (> 500 patients)

# Challenges in Current Drug Discovery Pathway



- 10 – 15 years
- Multi Billion Dollars
- A few % successful rate

# Combinational Drug for COVID-19

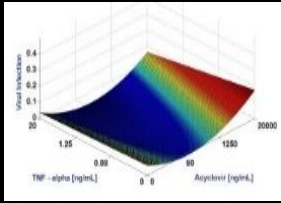
## - In vitro Test -

- A pool of 12 repurposed drugs was used to search for the optimal drug-dose combination against COVID.
- With 10 dosing levels for each of the 12 drugs, the drug-dose search space has  $10^{12}$  combinations.
- With the AI-PRS based *in vitro* test, top 793 mono- and multiple drug combinations were selected from the  $10^{12}$  search space within two weeks.
- Remdesivir (RDV) alone is somewhat efficacious and *in vitro* inhibition rate is 20%.
- Top killer combination (RDV+RTV+LPV) has inhibition rate near 100%.

Drug	Inhibition
Remdesivir (RDV): 0.9 $\mu$ M	21.1%
Remdesivir (RDV): 0.81 $\mu$ M	15.5%
Chloroquine (CQ): 0.071 $\mu$ M	1.4%
Ritonavir (RTV) 1.02 $\mu$ M	0.9%

Drug Combination	Inhibition
(RDV + RTV + LPV) + DEX (0.063 $\mu$ M)	96.6%
(RDV + RTV + LPV) + DEX (0.0315 $\mu$ M)	88.9%

# Simplicity and Complexity



AI - PRS Equation

$$E(C, t) = x_0 + \sum_{i=1}^N x_i c_i + \sum_{i=1}^N y_{ii} c_i^2 + \sum_{i=1}^{N-1} \sum_{j=i+1}^N z_{ij} c_i c_j \quad C_i : \text{dose}$$

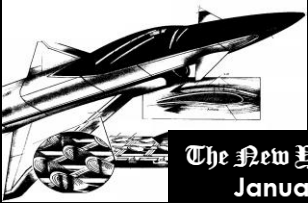
$x_0$ ,  $x_i$ ,  $y_{ii}$  and  $z_{ij}$  - dynamically vary with a specific diseased system

兵無常勢、水無常形、因敵變化而取勝 孫子兵法虛實篇

# Complex Systems

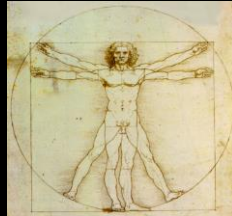
- Science Base -

## Turbulent Flow



The New York Times  
January 3, 1995

## Bio Systems



## Social Systems



- A large number of **interacting elements**
- Self-organized into a non-linear dynamic system
- The system **emerging properties** can **NOT** be step-by-step derived from these interacting elements
- Adaptability and robustness

Science Vol 284, April 2, 1999

Science Vol 325, July 24, 2009

## AI - PRS Equation

E =  
Emerging Property

$$x_0 + y_1 C_1 + y_2 C_2 + z_1 C_1^2 + z_2 C_2^2 + z_{12} C_1 C_2$$

Drug Molecules Interacting with Disease Elements



# Parting Remarks

Drug/Dose



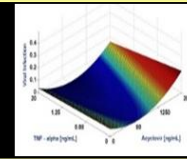
Efficacy / Toxicity

## AI Personalized Medicine

Drug / Dose



$$E(C, t) = x_0 + \sum_{i=1}^N x_i c_i + \sum_{i=1}^N y_{ii} c_i^2 + \sum_{i=1}^{N-1} \sum_{j=i+1}^N z_{ij} c_i c_j$$

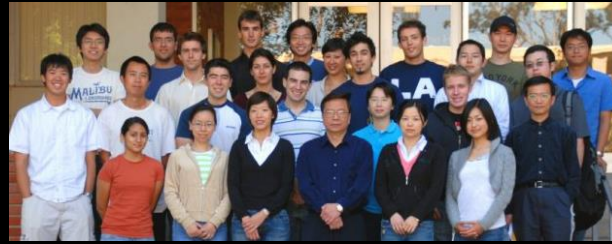


Efficacy / Toxicity

We Are All Parabolas

Life can be very simple!  
Do not make it too complex!

# Acknowledgements



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students

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