# The 4th SABPA Frontiers in Therapeutics & Diagnostics Forum

Note-taking: Eric Zhou, PhD

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**From viruses to immunology, the study of attack and defense**

David Baltimore, PhD
Nobel Laureate, Former President of California Institute of Technology

Dr. Baltimore went to college in 1956. Inspired by his summer at JaxLab in Maine, he decided on a career in experimental biology. During that pre-molecular biology era, Watson and Crick's discovery provided the link of the molecules and living systems.

In 1970, Dr. Baltimore found that cancer causing RNA virus has a DNA polymerase in the virus particles – reverse transcriptase, which violated crick's central dogma. This becomes a big surprise to the field. There are many implications for this discovery. 1) 5 years later, Dr. Baltimore was awarded Nobel Prize. 2) Viral genes could be integrated into cellular DNA. 3) Cancer was a disease caused by genes that control cell behavior. 4) Virus could be gene vectors, which lead to today's gene therapy. All of these discovery was before the time of DNA manipulation and recombination.

In 2006, Dr. Baltimore stepped down from the president of Caltech and moved to translational medicine focusing on bringing gene therapy to reality. Many new companies around the world today are developing gene therapies.

HIV was found to to be a retrovirus with reverse transcriptase. It eludes control by antibodies. Carbohydrates are covering most of the open surfaces. Therefore, it doesn't present protein epitope to the immune system. The challenge is that we still need a vaccine to prevent the spread of HIV even though we have good drugs.

T-cell based vaccines so far have failed, so we should focus on Ab based vaccines. Highly potent anti-HIV human monoclonal Abs have been isolated from infected people and studied in details. Dr. Baltimore developed vector immunoprophylaxis (VIP), a method to direct the body to make these monoclonal antibodies.

AAV mediated delivery of neutralizing antibodies as prophylaxis against HIV:
Engineering Ab production using AAV8
Pros: non pathogenic in humans, non-integrating DNA vector, excellent expression

AAV transfer vector: AAV2/8 is built from 5 virus
Using AAV2/8-mediated luciferase expression as a model system, when it is injected through IV, the virus goes to liver. When injected intramuscular, virus stays in muscle with very high expression. Amount of antibodies is related to the amount of virus injected, suggesting it is a well controlled system. High level of antibodies can be produced during the life of the mouse. Over 1 mg/mL.

Transfer Human PBMSc, -Challenge with HIV – sample weekly (looking for CD4 cells, because HIV kills CD4 cells), use this as a platform to evaluate antibodies.

Determination of the minimum protective VRC01 dose in vivo: 1.6 ug/uL of VRC01 was not sufficient to protect.

Conclusion: VIP is capable of protecting animals from X4 and R5 strains of HIV, including a transmitted molecular founder strain, and it protects humanized mice from mucosal challenge.

VIP protects NHPs from HIV challenge
Have done everything can think of in lab, can we do in human? Is it safe? For how long it works?

Transitioning to clinical development – teamed with the vaccine research center at NIH to test clinically the effectiveness of VRC07

VRC 603 trial shows safety the production of active VRC07. It also shows sustained production of more than 5 ug/uL, and characterized the immune response and the PK of VRC07 using an AAV8 vector. Results will be announced in just a couple of months.

VIP of other virus
VIP was developed to prevent HIV, could use for flu, or malaria. It is relatively cheap and quite stable, making it as stock piling against natural or bioterrorist mediated viral diseases.

After 60 years of research, we are from not understanding anything in 1960s to now taht we can manipulate.

**FDA approval for Mayzent (siponimod), the first oral drug to treat secondary progressive MS with active disease**

Shifeng Pan, PhD
Executive Director, The Genomic Institute of the Novartis Research Foundation

The project was started 17 years ago in La Jolla in 2002,
What we know at the project – FTY720 gilenya was effective in phase 2 trials in renal transplantation.
The MOA was unknown; it is different from classical immunosuppressant – rescue peripheral lymphocyte counts but no anti-proliferative activity
Adverse effect; transient reduction of heart rate after initial doses
Very long elimination half lives across species
No in vitro assay available. Although FTY720 is effective, it has a very bad drug like properties. But there is no other choice.

How do you start a program without in vitro assay?
Luckily, there is a convenient in vivo PD assay. After dosing the mice, we can count lymphocyte. At 6 hours, lymphocyte changed from >90% to ~10%.

Later, MOA was reported by two groups independently a few months after the program. As a prodrug for sphingosine kinase, it has a high binding affinity for hS1P2.
Hypothesized that introducing lipid tail rigidity may achieve desired properties.

NIBR652 in vivo PD ED50 0.1 mg/kg
NIBR 587 is found to be S1P1 selective. But amino phosphate group is problematic. So the group moved on to a non prodrug strategy. In 2003, the group kept the same hydrophobic core with positively and negatively charged groups with linkers. Amino carboxylates were used to mimic amino phosphates. The group identified a few good compounds, discovered BAF312, a less potent compound but it is in the right direction.

The group further added a CF3 group and replace a phenyl group with cyclehexyl group. 3 log potency improvement was achieved.

BAF312 is a potent S1P1 and S1P5 dual modulator
Acts as an S1P1 functional antagonist and an S1P5 agonist
PK-PD relationship of BAF312 in rats
Efficacious in Rat EAE model at 0.3 mg/kg

Clinical studies and its approval - The Mayzent journal
BAF312 has favorable PK in Humans = an apparent half life of 30 hr.
Leads to reduction of peripheral absolute lymphocyte counts in humans. Return to normal within weeks.
BAF312 shows first dose effects on heart rate – this almost stopped the program.
We understand it better why this happens. So the clinical team lead a dose titration studies to mitigate S1P1 effects on heart rate.

Phase 2 start in RRMS. 0 adaptive study design included intrim analysis.

2 mg dose selected for Phase 3.
Novartis decides to study second progressive MS to go after the medical needs.

A very large phase 3 study. The study recruited more than 1600 patients, represent typical SPMS population, where other treatments failed. The drug was approved in 2019.

**Moving PROTAC Protein Degraders from the Laboratory to the Clinic.**

Ian Taylor, PhD
CSO, Arvinas

Arvinas Company Overview
Founded in July 2013, September 2018 IPO, one of the first PROTAC in clinic.
High potential PROTAC pipeline, focused on cancer and neurology

PROTAC: Proteolysis targeting chimera, a small molecule induced degradation of disease causing protein by ubiquitin proteasome system. PROTAC combine the power of gene based medicines with the benefits of small molecule therapy. Overcome target protein overexpression and selectively eliminate mutated proteins.

Tenets of PROTAC degraders – resistance mutations, undruggable, protein aggregates, scaffolding function, isoform selectivity, gene amplification,

Two big questions: 1) Will a PROTAC have drug like properties? 2) In human, will a PROTAC be safe?

ARV-110 AR degrader for men with metastatic castration resistant prostate cancer (mCRPC)
15-25% patients responded.
Highly selective degrader of AR, DC50 = 1 nM
In vitro studies degraded 95% - 98% of AR in multiple cell lines typically used in prostate cancer research. ARV 110 inhibits AR dependent tumor growth in xenograph models with oral, daily dosing.

First patient dosed March 2019
Design 3+3 dose escalating starting 35 mg.
Objective: max tolerance, PK, anti-tumor activity, biomarkers.
ARV-110 phase 1 dose escalation, PK is dose proportional. Overall favorable profile

ARV471 ER degrader for patients with locally advanced or metastatic breast cancer
In vivo model, oral daily dose of ARV471 inhibited tumor growth by 99% at 10 mpk and 106% at 30 mpk in a ESR1 mutant patient derived xerograph model.
In combination with palbociclib, ARV471 exhibits superior tumor shrinkage vs Fulvestrant
Orally dosed ARV471 shrinks tumor and robustly degrades ER in MCF7 xenografts.
Phase 1 started August 2019, max tolerated dose recommended phase 2 dose safety, PK, anti-tumor activity, biomarkers.

The third big question will a PROTAC demonstrate efficacy in patients- will be released in major conferences.

**In cancer as in real estate, location matters: The role of extrachromosomal oncogene amplification in cancer**

Paul Mischel, PhD, Professor, UCSD, Scientific Founder of Boundless Bio

Extrachromosomal DNA in cancer: ecDNA enables copy number change in response to environment changes.
This mechanism of inheritance enables explosive growth in copy number while maintaining heterogeneity, enabling rapid evolution.
Circular DNA favors rapid change, ecDNA favors evolution.

What is the shape of ecDNA? Optical mapping of long fragments of DNA up to 250 kb to resolve ecDNA structure. Scanning EM shows ecDNAs are circular like donuts.
Oncogenes encodied in ecDNA are within the top 1% of the most highly transcribed genes in tumor genomes

ecDNA drives high level of transcription because of they are so many copies of the DNA template.

There is enhanced chromatin accessibility in ecDNA
ecDNAs are the most accessible chromatin in the genomes of actively cycling cancer cells.
ecDNA – lower order of compaction.
ecDNA has increased distal interactions, as demonstrated by Hi-seq.
The circular shape of ecDNAs may potentially lead to changes in the cis regulation.

Boundless bio is building a next gen precision oncology company by changing the architecture of gene regulation

**Human microbial diagnostics and therapeutics**

Jack Gilbert, PhD, Professor, the Scripps Institution of Ocoeanography

Immune system maintains the ecosystem in our body.
Microbiome wide association studies identify the association between microbial activities and human health and diseases
Bacteria are supplementing the proteins that are absent from our diets.
All people have a unique microbiome because each of us live a unique life.
The gut microbiome can explain significant variance in human phenotypes
Airway microbiota still differentiate asthma phenotypes
Surgical complications