Reverse Engineering Combination Therapies for Evolutionary Dynamics of Disease: An $\mathcal{H}_\infty$ Approach

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***Abstract*— We propose a general algorithm for the systematic design of feedback strategies to stabilize the evolutionary dynamics of a generic disease model using an $\mathcal{H}_\infty$ approach. We show that designing therapy concentrations can be cast as an $\mathcal{H}_\infty$ state feedack synthesis problem, where the feedback gain is constrained to not only be strictly diagonal, but also that its diagonal elements satisfy an overdetermined set of linear equations. Leveraging recent results in positive systems, we develop an algorithm that *always* yields a stabilizing controller.**

I. Introduction and Motivation

A challenge inherent to the treatment of certain infectious and non-infectious diseases, such as HIV or cancer, is the risk that the pathogen or tumor will *evolve away* and become resistant to treatment methods that comprise the standard of care. Especially vulnerable to this phenomenon are treatment methods that involve exposing the disease population (such as viruses or cancer cells) to single therapies for an extended period of time. In particular, this establishes an environment in which the occurrence of mildly drug resistant pathogens or tumor cells can develop a huge evolutionary advantage over the pathogens/tumor cells for which the monotherapy is targeted, leading to so called "treatment-escape."

This phenomenon has received considerable attention in the biology and biomedical communities. For example, the human immunodeficiency virus (HIV) has been shown to escape from anti-HIV monotherapies, whether they be a small molecule drug or an antibody. In cancer treatment, acquired tumor resistance arises with targeted drugs and cytotoxic chemotherapy, limiting their utility and requiring design of alternative drugs for resistant tumors. One of the solutions that has been proposed [1], [2] is the rational design of combination therapy, much in the spirit of highly active antiretroviral therapy (HAART), the current standard of care for the treatment of HIV.

Recent results by Rosenbloom, et al. [3] have been more quantitative in nature, modeling the evolutionary dynamics of HIV and showing through simulations how the effect of antiretroviral dynamics can determine HIV evolution and therapy outcome. The Michor lab [4] recently showed the effects of different *erlotinib* dosing strategies in the presence of pharmacokinetic fluctuations on the evolution of resistance of non small cell lung cancer through simulations of a stochastic evolutionary dynamics model.

Although these methods have provided some insight into the problem, the challenge of designing treatment protocols that prevent escape is really one best addressed by control theoretic methods. Recent results in this spirit, especially targeted at cancer therapy, apply methods from optimal and receding horizon control [5], [6], as well as gain scheduling techniques [7], to synthesize treatment protocols that are robust to parameter uncertainty, an inherent issue in all biological systems.

As of yet, however, no methods exist for a principled design of targeted combination therapy concentrations that *explicitly* account for the inherent evolutionary dynamics of a system. The main contribution of this paper is a general algorithm for the systematic design of feedback strategies to stabilize the evolutionary dynamics of a generic disease model using an $\mathcal{H}_\infty$ approach.

In particular, we observe that designing antibody concentrations can be cast as an $\mathcal{H}_\infty$ state feedback synthesis problem, where the feedback gain is constrained to not only be block diagonal, but also that each block diagonal element be identical. Leveraging recent results in positive systems [8],[9], we develop an algorithm that always yields a sub-optimal, but stabilizing controller.

Our algorithm has applications in combination targeted cancer therapy [10], antibody therapy of cancer [11], antibody and/or drug therapy of HIV [12], as well as many other problems in which mutation, selection, and escape are dominant features of the dynamics.

The structure of the paper is as follows. In Section II, we fix notation, introduce a simplified generic evolutionary dynamics model that encodes replication, mutation and neutralization, and summarize relevant results from the positive systems literature. Section III presents our combination therapy synthesis algorithm. Section IV illustrates the effectiveness of our algorithm on an HIV antibody therapy design problem, and Section V ends with concluding remarks and directions for future work.

II. Preliminaries

A. Notation

$\mathbb{R}_+$ denotes the set of nonnegative real numbers. The inequality $X > 0, (X \geq 0)$ means that all elements of the matrix (or vector) X are positive (nonnegative). $X \succ 0$ means that X is a symmetric and positive definite matrix. A matrix $A \in \mathbb{R}^{n\times n}$ is said to be *Hurwitz* if all eigenvalues have

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negative real part. Finally, the matrix is said to be *Metzler* if all off-diagonal elements are nonnegative.

B. Problem formulation

The quasispecies model [13] was formulated to describe the dynamics of populations of self replicating macromolecules undergoing mutation and selection, and to analyze how steady state population distributions change with increases in mutation rates. We choose this model for both its relative simplicity and for its ability to capture the salient features of the evolutionary dynamics of a simplified generic disease model. To incorporate the effects of potential therapies into the basic quasispecies model, we define a generic binding neutralization reaction, $\ell + \mathrm{x} \longrightarrow_{K_A} \ell \cdot \mathrm{x}$ – neutralizing macromolecule ℓ binds to self replicating macromolecule x with association rate K_A, giving a neutralized complex $\ell \cdot x$. The quasispecies model is written as

$$\dot{x}_i = (r_i q_{ii} - d_i)x_i + \sum_{k \neq i}^{n} r_i q_{ki} x_k - \sum_{k=1}^{m} \psi_{ki} \ell_k x_i \quad (1)$$

where $x_i \in \mathbb{R}^n_+$ is the concentration of mutant i, $\ell_k \in \mathbb{R}_+$ is the concentration of neutralizing macromolecules (assumed to remain at constant concentrations throughout), r_i and d_i are the replication and degradation rates, respectively, of mutant i, and q_{ki} is the probability that mutant i mutates to mutant k. Finally, $\psi_{ki} = f(K_{ki})$ is a function of the association constant K_{ki} for each neutralization reaction representing the rate at which a neutralizing macromolecule ℓ_k neutralizes mutant i. The rates r_i and ψ_{ki} can be viewed as replication and neutralization fitnesses of mutant i.

The following state space representation of equation (1) outlines the inherent feedback of the system induced by these neutralization reactions:

$$\begin{aligned} \dot{x} &= (A - \Psi L)x + w \\ z &= \overline{\Psi} L x \end{aligned} \quad (2)$$

with (i) $A \in \mathbb{R}^{n \times n}$, with $A_{ij} = r_i q_{ij} \geq 0 \ \forall \ i \neq j$ and $A_{ii} = r_i q_{ii} - d_i$, that encodes the replication and mutation dynamics; (ii) Ψ, $\overline{\Psi} \in \mathbb{R}^{n \times nm}$ block diagonal matrices that describe the fitness of n mutants with respect to m different neutralizing macromolecules, with diagonal elements $\Psi_i = (\psi_{ik}) \in \mathbb{R}^{1 \times m}_+$ and $\overline{\Psi}_i = (\frac{1}{\psi_{ik}}) \in \mathbb{R}^{1 \times m}_+$; (iii) $L = (I \otimes \ell) \in \mathbb{R}^{mn \times n}_+$, with $\ell = (\ell_k) \in \mathbb{R}^m$, a block diagonal matrix that encodes the concentrations of neutralizing macromolecules for all n mutants; and (iv) $w \in \mathbb{R}^n_+$ an arbitrary positive disturbance. Note that $\Psi L, \overline{\Psi} L \in \mathbb{R}^{n \times n}_+$ are by construction strictly diagonal matrices.

We set the regulated output $z = \overline{\Psi} L x$ as a proxy to minimizing the concentration of neutralizing macromolecules needed to robustly stabilize the system. The introduction of the weighting matrix $\overline{\Psi}$ is such that control components corresponding to more neutralizing antibodies are less penalized than those of less neutralizing ones.

Remark 1: $A > 0$ and the off diagonal entries are several orders of magnitude smaller than the diagonal entries. This is due to the biological fact that mutation rates range from $10^{-5} - 10^{-9}$ mutations per base pair per replication cycle for reverse transcriptase to DNA replication.

Letting G denote the closed loop system (2), the control task then becomes to reverse engineer neutralizing macromolecule concentrations by finding a controller $K = (I \otimes \ell)$ that leads to a stable G satisfying $||G||_\infty < \gamma$, for some robustness level $\gamma > 0$.

C. The bounded real lemma for internally positive systems

Recent results by Tanaka and Langbort [8] and Rantzer [9] on the synthesis of $\mathcal{H}_\infty$ controllers for positive systems show that the design of structured static state feedback controllers for internally positive systems can be reformulated as a convex problem. In this section we provide a brief survey of the relevant definitions and results from [8]:

Definition 1: The LTI system

$$\begin{aligned} \dot{x} &= Ax + Bw \\ z &= Cx + Dw \end{aligned} \quad (3)$$

with $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times q}$, $C \in \mathbb{R}^{p \times n}$ and $D \in \mathbb{R}^{p \times q}$ is called *internally positive* if for every $x_0 \in \mathbb{R}^n_+$ and all inputs such that $w(t) \in \mathbb{R}^q_+$ for all $t \geq 0$, the state vector $x(t)$ belongs to $\mathbb{R}^n_+$ and the output vector $z(t)$ belongs to $\mathbb{R}^p_+$ for all $t \geq 0$.

The internal positivity of a system is easily determined by a simple condition on its system matrices:

Lemma 1: System (3) is internally positive if and only if

1) A is Metzler, and
2) $B, C, D \geq 0$, i.e. matrices B, C, and D are entry-wise non-negative.

In light of this result, it is easy to show that system (2) is internally positive:

Lemma 2: System (2) is internally positive.

Proof: Condition 2) of Lemma 1 is easily seen to be satisfied by noting that in (2), $B = I$, $C = \overline{\Psi} L$ and $D = 0$. To see that $A - \overline{\Psi} L$ is Metzler, it suffices to notice that since $\overline{\Psi} L$ is strictly diagonal, it cannot affect the Metzler property of A. ∎

Systems that are internally positive enjoy the significant advantage that the storage function matrix used in the bounded real lemma to characterize the $\mathcal{H}_\infty$ norm of a system via a semi-definite program (SDP), can be taken without loss to be diagonal, as outlined in the following theorem, slightly modifed from [8].

Theorem 1: Let the system (3) be internally positive with (A, B) stabilizable and (C, A) detectable. Let the corresponding transfer function be given by $G(s) := C(sI - A)^{-1}B + D$. Then the following statements are equivalent:

1) $\|G\|_\infty < \gamma$ and A is Hurwitz;
2) There exists a diagonal matrix $X > 0$ such that

$$\begin{bmatrix} A^T X + XA + C^T C & XB + C^T D \\ B^T X + D^T C & D^T D - \gamma^2 I \end{bmatrix} \prec 0. \quad (4)$$

The fact that X can be restricted to be diagonal is very useful in synthesizing *structured* feedback controllers, when this structure is defined by *sparsity* in the feedback gain. Our setting, however, requires not only sparsity, but a type

of algebraic consistency, as $K = I \otimes \ell$ implies that each block diagonal element of K must be equal. Unfortunately, there is no known way of enforcing this additional coupling in a convex manner.

III. A Sub-optimal $\mathcal{H}_\infty$ combination therapy controller

In this section, we deal with the aforementioned non-convexity of the optimal control problem by formulating an iterative algorithm for finding effective antibody concentrations, exploiting the internal positivity of the system to show that it always yields a stabilizing controller.

A. Stabilizing controller

We begin with a simple algorithm for the synthesis of stabilizing controller for the nominal system, which admits a particularly simple formulation in light of the Metzler nature of A.

Lemma 3: There exists $\epsilon > 0$ such that the solution to the convex program:

$$\begin{aligned} &\text{minimize } _{\ell \in \mathbb{R}^m_+} ||\ell||_\infty \\ &\text{subject to} \\ &A_d + \epsilon I - \Psi L \prec 0 \\ &L = I \otimes \ell \end{aligned} \tag{5}$$

is a stabilizing controller for system (2), where A_d is a diagonal matrix comprised of the diagonal elements of A.

Proof: Rewrite $A = A_d + M$ where A_d is diagonal and $M = \{m_{ij}\} \in \mathbb{R}^{n \times n}$, $m_{ij} = 0$ for $i = j$ and $m_{ij} > 0$ for $i \neq j$. By the Perron Frobenius theorem, there exists $r > 0$ such that the spectral radius $\rho(M) = r \leq \max_i \sum m_{ij}$. Let $\epsilon = \max_i \sum m_{ij}$ and rewrite $M = \epsilon I - (\epsilon I - M)$. We note that $-(\epsilon I - M) \prec 0$. The closed loop dynamics are then given by $A - \Psi L = A_d + \epsilon I - (\epsilon I - M) - \Psi L \prec A_d + \epsilon I - \Psi L \prec 0$, yielding the desired stability. ∎

Remark 2: The stabilization problem can be solved independently of a storage function because it can be reduced to satisfying element wise inequalities.

B. A Suboptimal $\mathcal{H}_\infty$ combination therapy controller

Observe that through a straightforward application of (4) to system (2), the antibody concentrations ℓ yielding an optimal $\mathcal{H}_\infty$ closed loop norm can be found by solving the following non-convex program:

$$\begin{aligned} &\text{minimize } \gamma \\ &\text{subject to} \\ &\begin{bmatrix} A_{cl}^T X + X A_{cl} + (\overline{\Psi} L)^T (\overline{\Psi} L) & X \\ X & -\gamma^2 I \end{bmatrix} \prec 0 \\ &A_{cl} = (A - \Psi L) \\ &L = I \otimes \ell \\ &X \succ 0,\ X \text{ diagonal} \end{aligned} \tag{6}$$

Applying a Schur Complement to $A_{cl}^T X + X A_{cl} + (\overline{\Psi} L)^T (\overline{\Psi} L)$ yields the more amenable form

$$\begin{aligned} &\text{minimize } \gamma \\ &\text{subject to} \\ &\begin{bmatrix} A_{cl}^T X + X A_{cl} & X & (\overline{\Psi} L)^T \\ X & -\gamma I & 0 \\ \overline{\Psi} L & 0 & -\gamma I \end{bmatrix} \prec 0 \\ &A_{cl} = (A - \Psi L) \\ &L = I \otimes \ell \\ &X \succ 0,\ X \text{ diagonal} \end{aligned} \tag{7}$$

Remark 3: We can impose an additional constraint limiting the concentrations of candidate therapies. This is necessary with certain drugs that have maximum tolerated doses dictated by clinical trials.

Thus the only non-convexity remaining are the product terms between the storage function matrix X and the controller gain L in $A_{cl}^T X + X A_{cl}$. As mentioned earlier, there are no known convex reformulations of this problem due to the additional structure on L. As such, we suggest the following iterative algorithm, based on the convex programs (5) and (7), to find a stabilizing controller.

For ease of notation, let $\mathrm{P}_{X'}(\ell, \gamma)$ denote that we solve (7) with $X = X'$ fixed, and that we optimize over ℓ and γ. Similarly, let $\mathrm{P}_{\ell'}(X, \gamma)$ denote that we solve (7) with $\ell = \ell'$ fixed, and that we optimize over X and γ. Additionally, let $(Z, \gamma) = \mathrm{P}_{Z'}(Z, \gamma)$ denote the solutions to the respective programs, for $Z, Z' \in \{X, \ell\}$.

We are now in a position to present our algorithm:

Algorithm 1 Combination Therapy

1) Set $\epsilon > 0$
2) Solve (5) to obtain an initial stabilizing controller ℓ'.
3) while $\gamma' - \gamma > \epsilon$:
   i) Set $(X', \gamma) = \mathrm{P}_{\ell'}(X, \gamma)$.
   ii) Set $(\ell', \gamma) = \mathrm{P}_{X'}(\ell, \gamma)$.
   iii) Set $\gamma' = \gamma$.

Proposition 1: Algorithm 1 always converges to a feasible γ and generates a stabilizing controller for (2).

Proof: By Lemma 3, an initial stabilizing controller can always be found, and thus the algorithm can always be initialized. The sequence of γs then defined by the iterative process in Algorithm 1 is non increasing by construction, and bounded below by 0, thus implying convergence. We therefore have that our algorithm always converges to a local minimum value of γ, and yields a set of gains which, by the bounded real lemma, robustly stabilize system (2). ∎

IV. HIV/Antibody Therapy Application

Our results provide a principled approach to the design of antibody treatments for chronic infection with human immunodeficiency virus-1 (HIV-1). We illustrate this with an example motivated by experimental results of evolutionary dynamics of HIV-1 in the presence of antibody therapy obtained in [14].

A relatively recent discovery is that a minority of HIV-infected individuals can produce broadly neutralizing antibodies (bNAbs), that is, antibodies that inhibit infection by many strains of HIV [12]. These have been shown to inhibit infection by a broad range of viral isolates in vitro but also protect non-human primates against infection [12],[15], [16]. Recent experimental results conducted by Florian Klein, et al. in the Nusswenzeig lab at Rockefeller University have demonstrated that the use of single antibody treatments can exert selective pressure on the virus, but escape mutants due to a single point mutation can emerge within a short period of time [14]. Although antibody monotherapy did not prove effective, it was shown that equal, high concentrations of an antibody pentamix effectively control HIV infection and suppress viral load to levels below detection. The goal of this example is to demonstrate how our proposed algorithm offers a principled way to design combination antibody therapies that control HIV infection and prevent evolution of any set of known resistant mutants. In a realistic setting, the ability to do this relies on the knowledge of what resistant viruses may be selected for with single therapies, and so this algorithm would be most effective in conjunction with single antibody selection experiments.

1) Model parameters: We consider a system of eighteen HIV mutants with five potential antibodies to use in combination. Figure 2 lists the mutants considered in this example with their corresponding half maximal inhibitory antibody concentration (IC50) in $\mu g/ml$, as measured by the Nussenzweig lab in [14]. Antibodies 3BC176, PG16, 45-46G54W, PGT128 and 10-1074 are potential combination therapy candidates.

Although virus replication rates can vary considerably depending on the nature of the mutations a virus may undergo, we choose replication rates to be $0.5\ (\mathrm{ml}\cdot\mathrm{day})^{-1}$ for all mutants. We justify this selection by noting that escape mutants grew to be dominant mutants during selection experiments and assume that replication rate variability due to mutations were negligible.

The fitness function associated with the neutralization of a virus i with respect to an antibody j is a Hill function $\psi_{ij} = \frac{\ell_j^n}{\ell_j^n + K_{ij}^n}$ where n is the Hill coefficient, ℓ_j is the concentration of a given antibody j, and $K_{ij} = \frac{k_{on}}{k_{off}} = \frac{[x_i \ell_j]}{[x_i][\ell_j]}$ is the association constant for the virus/antibody binding reaction $\ell_j + \mathrm{x_i} \longrightarrow_{k_{on}} \ell_j \cdot \mathrm{x_i}$, and k_{on} and k_{off} are the on and off reaction rate constants. Note that the association constant represents the fraction bound of antibody/virus complexes in solution and that $K_{ij} = \frac{3 \cdot \mathrm{IC50}_{ij}}{3r_i + ln(2) - \mathrm{IC50}_{ij}}$, is found by solving Equation 1 for one virus/antibody pair for the duration $[t_0, t_f] = [0, 3]$. We simplify the Hill function by setting the Hill coefficient $n = 1$, as there is evidence that that antibodies do not bind cooperatively. Our algorithm yields antibody concentrations near zero and this yields the linear approximation $\psi_{ij} = \frac{1}{K_{ij}} \ell_{ij}$. In addition, the antibodies we consider in our example do not target the same epitope, in other words, do not bind competitively to the same sites on the virus, thereby reducing any coupling between antibody concentrations.

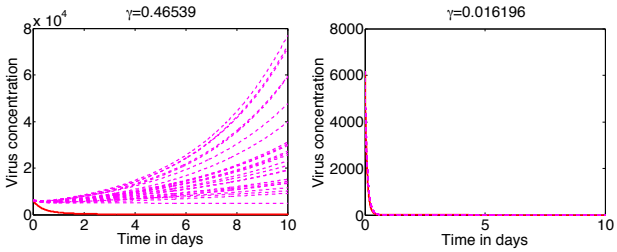

Fig. 1. (Left) Sum of virus populations over time for the nominal closed loop controller (solid red) and for random time invariant perturbations in the dynamics with the same controller (dashed magenta). (Right) Sum of virus populations over time for the robust closed loop controller (solid red) and for random time invariant perturbations in the dynamics with the same controller (dashed magenta).

The mutation rate for HIV reverse transcriptase is $u = 3 \times 10^{-5}$ mutations/nucleotide base pair/replication cycle, and the HIV replication cycle is approximately 2.6 days. We approximate the rate of mutation for a particular amino acid mutation at a particular location to be $\frac{1}{n_a} u(1-u)^k = 1.443 \times 10^{-6}$ per replication cycle, where $k \approx 3000$ is the size of the genome in residues and $n_a = 19$ is the number of amino acids that can be mutated to. We do not consider back mutations, as the probability of mutation is negligible.

Units of concentration in number of viruses/ml or number of antibodies/ml are used for states, and time is measured in days. The standard volume is 1 ml.

2) $\mathcal{H}_\infty$ controller: We synthesized a nominal stabilizing controller according to (5) and found stabilizing antibody concentrations $L_s = \{0.0125, 0.0125, 0.0125, 0.0125, 0.0125\}$ in $\mu g/ml$ for antibodies {3BC176, PG16, 45-46G54W, PGT128, 10-1074}. Using Algorithm 1 with antibody constraints $L \leq 1$ $\mu g/ml$, we synthesized a robust controller yielding antibody concentrations of $L_r = \{1, 0, 0.003, 0.0031, 0.0026\}$. The closed loop $\mathcal{H}_\infty$ norm of the stabilizing controller was found to be $\gamma_s = 0.4$ whereas that of our robust controller had a norm of $\gamma_r = 0.016$. The simulations in Figure 1 illustrate the need for robustness in the face of model uncertainty – the robust controller remains stabilizing in the presence of small additive model uncertainty in the mutation and replication parameters of the system, whereas the nominal stable controller fails to do so. Note that Algorithm 1 converged to this robust controller after nine iterations in 38.514 s.

V. Conclusion and Future Work

We proposed an iterative algorithm for the systematic design of feedback strategies to stabilize the evolutionary dynamics of a generic disease model using an $\mathcal{H}_\infty$ approach. In particular, we reduced the problem to a non-convex $\mathcal{H}_\infty$ state feedack synthesis problem, where the feedback gain is constrained to not only be block diagonal, but also satisfy an additional algebraic constraint, namely that each block diagonal element be equal. Leveraging recent results in positive systems [8], we showed that our iterative procedure

always yields a stabilizing controller. Additionally, through an HIV inspired simulation example, we show that our method also results in a controller with useful robustness properties.

There are many promising avenues for future work. One is expanding the evolutionary dynamics model to include aspects that are more closely related to an animal model, such as pharmacokinetics and immune system dynamics. This will allow for the control design procedure even more applicable to personalized treatment protocol design. Another yet is the support of larger scale systems through a linear programming formulation of the distributed control problem for positive systems [9].

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Mutation	3BC176 IC50 $\mu g/ml$	PG16 IC50 $\mu g/ml$	45-46G54W IC50 $\mu g/ml$	PGT128 IC50 $\mu g/ml$	10-1074 IC50 $\mu g/ml$
WT	0.319	0.612	0.024	0.169	0.312
G471R	0.159	0.154	0.008	0.02	0.091
N160K	0.145	50	0.007	0.086	0.155
T162N	0.154	50	0.013	0.166	0.175
N279H	0.209	0.294	50	0.064	0.177
N280Y	0.276	0.145	50	0.031	0.126
N332K	0.232	0.988	0.017	50	50
N332Y	0.269	0.632	0.01	50	13.596
S334N	0.218	0.615	0.02	50	7.308
Y61H	0.243	0.285	0.015	0.098	0.26
E102K	0.173	0.341	0.023	0.11	0.207
N295S	0.347	0.5	0.017	0.145	0.159
I311M	0.23	2.67	0.013	0.248	0.253
S365L	0.26	0.273	0.009	0.045	0.153
G366E	0.187	0.167	0.001	0.021	0.074
I371M	0.2	0.303	0.013	0.064	0.164
N413K	0.188	0.557	0.014	0.032	0.109
E429K	0.146	0.503	0.017	0.082	0.167

Fig. 2. IC50 values for the indicated antibodies for mutant viruses found in continuous antibody monotherapy experiments conducted by the Nussenzweig lab at Rockefeller University [14]. WT signifies the the 'wild type' YU2 laboratory strain of clade B replication competent HIV. Mutations are labeled by the amino acid occurring in the WT strain, followed by the location of the amino acid and the amino acid mutation. Each mutation was found by doing a selection experiment: a humanized mouse was infected with monoclonal YU2 strain and given continuous mono therapy of either 3BC176, PG16, 45-46G54W, PGT128 or 10-1074. Mutant resistant viruses emerged as a result of these selection experiments and IC50s values were measured.