Just – Evotec Biologics

AI-Derived Antibody Discovery - Humanoids for Global Good
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• Using human faces as an example:
• Lightly train a Discriminator neural network on real human faces
• A generator begins generating images that sometimes fools the discriminator, and slowly learns to better fool the discriminator
• Continue training the discriminator with real human faces, forcing the generator to improve
• Eventually the generator can fool both discriminator and humans

J.HAL℠ utilizes Generative Adversarial Networks (GAN) to create synthetic realistic outcomes

GAN generators output results trained to fool a trained discriminator
J.HAL℠ technology is a GAN application for antibody sequences

Trained on real mature human antibody sequences

- Large, human-derived antibody sequence training set extracted from OAS
- Abacus™ is used to clean, analyze, classify, and place sequences into structure positions
- GAN training models are germline specific
- Ability to generate synthetic humanoid large, diverse, combinatorial germline pairings for library creation
- GAN-generated antibodies represent B-cell response – including full SHM
Antibody display library screening workflows

DNA sequencing is performed at most steps for panel identification

GAN Designs

DNA library synthesis

Phage

Phagemid

Fab library

Enrich for target binding Fabs

Fabs to IgG transient expression

Kinetics screen

Therapeutic mAb candidate

Yeast

Exp. Vector

scFv library

FACs

Option

Kinetics screen

Biophysical and Activity screen

scFv candidate

GAN refinements:
- Transfer learning
- Biasing

Yeast

Exp. Vector

IgG library

FACs

IgG secretion

option

Kinetics screen

Biophysical and Activity screen

Therapeutic mAb candidate
Screening the initial J.HAL library against SARS-CoV-2 RBD resulted in several panning hits

- 3 rounds of panning performed
- 176 clones sequenced – 35 were unique
- 22 were positive to SARS-CoV-2 Wuhan RBD in phage ELISA (“hits”)
- 8 hits also bound SARS-CoV-2 B.1.1.7 Spike variant
- Further hits are being extracted
- Leads being tested for binding and activity against broader antigen panel

These Wuhan RBD hits cross react with UK variant
J.HAL℠ utilizes Transfer Learning to bias the output to desired properties

GAN generators may then output focused and purposeful results based on broader training sets

- Use an existing trained GAN
- Supply faces with desired property
- The GAN learns this new property
- The output of the GAN is shifted, or biased, toward the new property

![Diagram showing the process of biased generation using Transfer Learning.](https://thispersondoesnotexist.com/)
GANs control design through transfer learning

This allows us to shift the generator for desired properties

- Properties are transfer learned by further training the existing GAN with sequences which exhibit the desired property
- The mechanism of the property could be known or unknown
- A known mechanism could be CDR length, charge, pl, predicted immunogenicity, etc.
- An unknown mechanism could be temperature or pH stability, long pharmacokinetics, etc.
- J.HAL℠ under continuous development and growth
Ultra High Throughput Method Development – Christine Siska

Biasing the library for favorable biophysical characteristics

- Using model proteins, determine **stress** conditions that distinguish between favorable and unfavorable molecules displayed on phage or yeast
- Develop a **capture** and purification mechanism that will bin displays based on resistance to stress conditions
- Next gen **sequencing** will be utilized to link library genotype to phenotype of each bin
- Data can be used for machine learning to guide GAN to generate more manufacturable mAbs
- Begin with heat denaturation in phage display

**Model Proteins with decreasing thermal stability**

- Atezoliz
- Nataliz
- Liril
- Ocreliz
- Olara

**Anti-Fab capture mechanism isolates folded Fabs after stress**

**Percentage Phage Remaining After 80C Incubation**

Fab sequences that are resistant to thermal denaturation are enriched in a mixture

**Sequence composition of mixture heated to 80C**

- atezolizumab
- lirilumab
- natalizumab
- ocrelizumab

**Ultra High Throughput Method Development**

– Christine Siska

Biasing the library for favorable biophysical characteristics
Purposeful hypothesis-driven GAN biasing is a tremendous tool for the exploration of antibody development and *in vivo* behavior.

The results lend themselves to the elucidation of first principles causes.

- Sequences with observed properties may be used to bias the GAN to generate a larger, diverse set of sequences which is biased toward or away from that property.
- Applications could include variable domain impact on
  - Conformational stability
  - Colloidal stability
  - Host cell protein interactions
  - Blood-brain barrier passage
  - Pharmacokinetics, including target-mediated effects, intracellular trafficking, in-serum stability
  - Effector function
  - Glycosylation
  - Tissue sequestering
  - PTMs
  - …
Questions?

- How are you building sequence sets with associated data to transfer learn?
- How are you pursuing some of the more difficult properties such as PK?
- Do your current library antibodies display improved properties?
- Can we give you massive amounts of cleaned data to help your transfer learning efforts?
- Could the GAN technology be applied to other biologics formats?
- Can you use the GAN methodology to improve existing antibodies?
- Can I come work with you at Just – Evotec Biologics?
- How can we collaborate?
- Can we start a discovery project with you?
Your contact:

Randal R. Ketchem, Ph.D.
VP of Molecular Design
randal.ketchem@just.bio