Project H)

Crowd-Sourcing Responders-

Robert Plenge

Asst. Professor Rheumatology at Brigham &Women's, Broad Institute

Background: One promise of personalized medicine is to predict which patients will respond to medications and which patients will not. To date, there are very few examples of robust genetic predictors of response to any medication. For one chronic disease, rheumatoid arthritis (RA), strong immunosuppressive medications are administered to patients in order to treat pain and inflammation. These drugs include biological agents that block the inflammatory cytokine TNF (anti-TNF therapy). Unfortunately, there are no reliable biomarkers to predict which 30% of patients will enter clinical remission following treatment with anti-TNF therapy. As a consequence, a large number of patients are exposed to anti-TNF therapy without benefit, putting them at risk for infections and other complications while failing to control their symptoms. During this time, uncontrolled inflammation leads to irreversible joint damage and systemic inflammation, which ultimately leads to severe disability and early mortality. Moreover, anti-TNF drugs are extremely expensive, costing each patient almost $20,000 for one year of treatment. Thus, a reliable predictor of response to anti-TNF therapy would have a major health and economic impact.

We believe the time is right to try a different approach to develop a biomarker predictor with a crowd-sourced collaborative study. We propose a "Challenge", where teams from across the world will compete to identify a genetic model that the high predictive value for response to anti-TNF therapy in RA patients.

Plan: There are two phases to our *anti-TNF Responder* Challenge. Phase I will use GWAS data from ~2,700 RA patients treated with anti-TNF therapy. Participants will use novel computational methods, together with previously unpublished genomic datasets (e.g., RNA-seq), to build polygenic predictors of response to anti-TNF therapy. Phase II will test polygenic models from Phase I in a completely independent GWAS dataset of ~1,100 RA patients treated with anti-TNF therapy (generated in collaboration with Consortium of Rheumatology Researchers of North America [CORRONA] and the Pharmacogenomics Research Network [PGRN]). The model with the greatest predictive value in Phase II will be declared the winner. We have partnered with *Nature Genetics* to publish the results of our *anti-TNF Responder* Challenge, with the winning team having a prominent role in the publication.

What we need now: While we have established the basic clinical question and have organized the initial GWAS and genomic datasets, we need input from Congress participants about how to make this a highly successful Challenge. We want to know: *Have we focused on the right clinical and biological question? How can we design the Challenge to encourage participation? Are there publically available genomic datasets that we should curate and make available to improve model building? Are there other genomic datasets should we generate? Are there ways we can get other academic, industry or patient-advocacy groups involved in our Challenge? Anticipating success, what would future Challenges look like?*

In addition, we want to expand the genomic datasets for the Sage Challenge. In particular, we would like to include genome-wide data (e.g., RNA-seq, GWAS, epigenetics) from RA patients on anti-TNF therapy and other immunosuppressive drugs. This could come from in-kind support from academic or industry groups that have already the data, or funding to help support data generation on existing biospecimens. As one example, through a collaboration with the Arthritis Foundation, Quest Diagnostics and the National Data Bank of Rheumatic Diseases, we have created the Arthritis Internet Registry (AIR). To date, nearly 4,000 patients have been enrolled, with ~20% providing biospecimens for genomic studies. In collaboration with the Broad Institute, we have the capacity to generate genomic data on AIR samples.

Long-term vision: The *anti-TNF Responder* Challenge is meant to be a starting point for a long-term collaboration among investigators to solve this vexing biological question. Over time, we hope to generate additional GWAS datasets on RA patients treated with anti-TNF therapy. We hope to expand this same approach to other DMARD therapy in RA, as well as similar biological therapy in other immune-mediated diseases. We expect results from the Sage Challenge will uncover novel biological pathways that will lead to novel hypotheses that must be tested in the future. For example, if we uncover a biological pathway that predicts non-response to anti-TNF therapy, then we will want to think about how to develop drugs that target that pathway to treat refractory patients.

Over to You

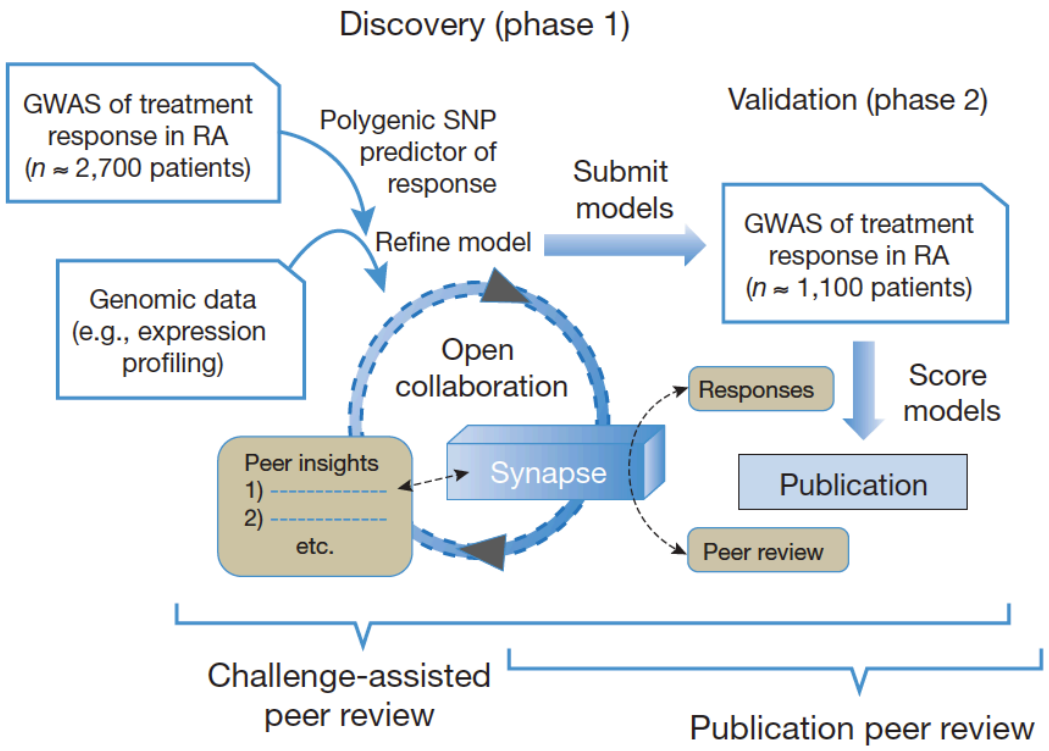
H- Crowd-Sourcing Responders

G	Organization	Last name	First
H	H3 Biomedicine	Barros	Luis
H	USAID	Bess	Cameron
H	J&J	Dobrin	Radu
H	Fanconi Anemia Research Fund	Hays	Laura
H	Sanofi-Aventis	Hugh-Jones	Charles
H	National Brain Tumor Society	Knight	Kris
H	Novo Nordisk	Kutlu	Burak
H	Consultant	Lieu	Charlie
H-Anchor	Sage Bionetworks	Mangravite	Lara
H	Stanford University	Morgan	Alexander
H	Pfizer	Naeve	Greg
H-Lead	Brigham & Women's	Plenge	Robert
H	National Brain Tumor Society	Rhee	Michele
H	UCSF	Risch	Neil
H	Vall D'Hebron, Spain	Tabernero	Josep
H	My Tomorrows	ter Wengel	Nathalie
H	National Brain Tumor Society	TonThat	N. Paul
H	H3 Biomedicine	Warmuth	Markus
H	Pfizer	Wood	Tony

Responders Challenges
Robert Plenge, Brigham & Women's Hospital

The DREAM Challenge:

Identify genetic predictor of response to anti-TNFα therapy for treatment of Rheumatoid Arthritis.



Plenge et al, Nature Genetics. May 2013

Potential alignment with existing Commons' approaches

Challenge Paradigm

Building communities

Synapse for data and code sharing

Governance for data sharing

Unmet needs and issues

Ask the question the right way that defines our goals:

- **Primary goal: Specific question of how to model a specific trait**
- **Secondary goal: Build a community that can work together to determine how to move this project forward beyond the narrow goals of this Challenge.**
- **Third goal: Use case for building communities on Synapse.**

Incentives to Participate:

- **Stakeholders: Modelers, Biologists, Clinicians, Advocates, Citizens.**
- **Participation means many different things.**
- **Make it easy to for people to contribute across disciplines.**
- **Social Networking**
- **Community building tools**

1-year vision for the future of this project

Complete Phase 1 of this Challenge

Have built an active community

Develop the goals for Phase 2