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PRINCIPAL INVESTIGATOR: Theodore Jardetzky

CONTRACTING ORGANIZATION: Stanford University
Palo Alto, CA 94304

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Theodore Jardetzky

E-Mail:tjardetz@stanford.edu

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13. SUPPLEMENTARY NOTES

14. ABSTRACT Omalizumab is currently the only FDA approved monoclonal anti-IgE therapy. We solved the IgE:omalizumab crystal structure to 2.54 Å. This structure elucidates the mechanism of omalizumab inhibition of IgE:FcεRIα and IgE:CD23 interactions, and explains omalizumab's selectivity for free circulating IgE. Surprisingly, the complex structure shares significant similarity with the disruptive IgE inhibitor E2_79, and provides mechanistic insight into the efficiency with which disruptive inhibitors are able to bind to, and accelerate FcεRIα dissociation from preformed IgE:FcεRIα complexes. Structural information from the IgE:omalizumab complex was used to generate a point mutation in the IgE-Fc, yielding an omalizumab-resistant IgE. Omalizumab-resistant IgE, in combination with omalizumab, promotes the exchange of the IgE repertoire on human basophils. This combination treatment demonstrates the possibility of substituting rather than depleting the IgE repertoire, thereby exchanging harmful, allergen-specific IgE while maintaining endogenous IgE-dependent regulatory mechanisms that may further suppress the allergic response.

15. SUBJECT TERMS
Allergy, IgE, anti-IgE therapy, IgE repertoire exchange

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

IgE antibodies bind the high affinity IgE Fc receptor (FcεRI), found primarily on mast cells and basophils, and trigger inflammatory cascades of the allergic response. Inhibitors of IgE:FcεRI binding have been identified and an anti-IgE therapeutic antibody (omalizumab) is used to treat severe allergic asthma and is being used experimentally for the treatment of food allergies. However, improved therapeutics are needed for the treatment of allergies. We are taking a two-pronged approach to developing improved therapeutics. The first approach is based on our observations that a novel class of anti-IgE inhibitors (DARPins), which can actively take apart receptor complexes, exhibits improved therapeutic potency in a mouse passive cutaneous anaphylaxis model. We propose to develop novel antibody therapeutics with this disruptive activity using a systematic set of experiments. In our second approach, we are pursuing the identification of small molecule inhibitors of the IgE:receptor interaction, since this would potentially allow for the treatment of a broader patient population. We have developed and implemented novel assay tools and approaches to enable the discovery of small molecule inhibitors. We feel that both approaches have significant and complementary value and we have made good progress in our research in both areas during the past year.

2. KEYWORDS:

Allergy, IgE antibodies, high affinity IgE receptor, FcεRI, accelerated dissociation, high throughput screening

3. ACCOMPLISHMENTS:

Major goals and accomplishments

Overview of proposed task and current accomplishments		
Specific Aim 1: Development of a novel anti-IgE antibody with potent disruptive inhibitor activity	**Proposed timeframes**	**Current Status (12 months)**
Major Task 1: Generate and characterize novel bifunctional anti-IgE antibodies		
Subtask 1: Bispecific antibody protein expression and purification	1-12	Redirected effort to other approaches
Subtask 2: Bispecific antibody protein functional studies	12-24	Redirected effort to other approaches
Subtask 3: Isolation of antibodies using phage display	1-12	Completed
Subtask 5: Functional studies with phage-derived Fabs	12-24	Ongoing
Subtask 6: Production and characterization of bifunctional antibodies using phage-derived Fab	12-36	Ongoing
Subtask 7: Elicitation of site specific antibodies from boost-prime immunization	12-36	Redirected effort to other approaches
Subtask 4: Structural studies of Fab:IgE complexes	6-36	Completed structures of: IgE-Fc:omalizumab complexes, ligelizumab:IgE-Fc complexes Other structural studies in progress
Specific Aim 1 Milestones:		

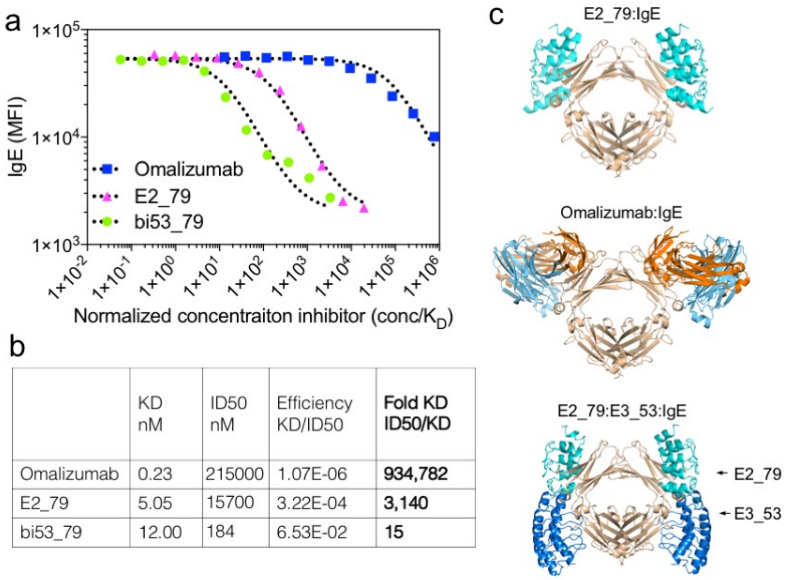
Milestone 1 Year 1: Express, purify and characterize chimeric omalizumab constructs	Month 10	In progress Redesigned strategy to use bifunctional omalizumab:DARPin constructs
Milestone 2 Year 1: Conduct phage display experiments with wt and mutant IgE-Fc	Month 10	Reached Obtained yeast display library, completed anti-IgE selection experiments
Milestone 3 Year 2: Analyze and optimize bispecific omalizumab and phage display anti-IgE constructs	Month 8	In progress Expressed evolved functional variants of omalizumab and demonstrated increased disruptive activity.
Milestone 4 Year 3: Complete structural analysis of anti-IgE complexes	Month 8	Completed structures of omalizumab:IgE complex; ligelizumab:IgE-Fc complex; Continuing to use EM and crystallography to study selected omalizumab variants.
Milestone 5 Year 3: Analyze anti-IgE immunization response, optimize best chimeric anti-IgE construct	Month 10	Redirected effort to alternative yeast-display approach.
Specific Aim 2: Identification and validation of candidate small molecule IgE inhibitors from high throughput screening.		
Major Task 2: Structure-function studies of small molecule lead compounds		
Subtask 1: Dose response screening of top (380) compounds from high throughput screening	1-8	Completed
Subtask 2: Functional studies of lead compounds using ELISA, cell-based and Biacore assays	6-24	Completed
Subtask 3: Binding and inhibition studies with analogs of candidate lead inhibitors	18-36	Completed
Subtask 4: Crystal structure analysis of lead compounds with IgE or receptor proteins	6-36	In progress. Pursued a fragment-based drug development approach; have obtained crystal structure of one of our leads bound to the IgE-Fc
Specific Aim 2 Milestones:		

Milestone 1 Year 1: Complete biochemical and cell-based inhibition studies with lead compounds from screening	Month 6	Completed
Milestone 2 Year 1: Complete direct SPR binding studies with lead compounds from screening	Month 8	Completed
Milestone 3 Year 2: Study top compound analogs in biochemical, cell-based and SPR binding assays.	Month 8	Completed
Milestone 4 Year 3: Complete structural analyses of lead compounds and analogs	Month 8	Ongoing

Specific Aim 1: Development of a novel anti-IgE antibody with potent disruptive inhibitor activity

Major Task 1: Generate and characterize novel bifunctional anti-IgE antibodies

Establishing a structural basis for understanding disruptive inhibitor efficiency. We have compared the disruptive inhibitor activity and structures of our three original anti-IgE inhibitors, E2_79, omalizumab and bi53_79 (Fig. 1a,b)[6-8], demonstrating the wide range of concentrations required for their ability to actively dissociate IgE:receptor complexes. As part of this proposal, we determined three new IgE complex structures to better understand the structural basis for these widely differing activities. One of these structures is the omalizumab:IgE-Fc complex, which we have already described in a publication[8], and the second consists of a ternary complex of E2_79, E3_53 and IgE-Fc (Fig. 1c), which mimics the bi53_79 DARPin that we have described previously. We are also in the process of completing the structure of a ligelizumab:IgE complex – ligelizumab is currently in clinical trials and represents one of the next generation anti-IgE therapeutics. Analysis of these complexes has provided a structural foundation for understanding how disruptive inhibitors may be re-engineered. We calculated the theoretical volumes of atomic overlap between omalizumab with FcεRI and E2_79 with FcεRI[8]. This analysis reveals that omalizumab has roughly three times the volume of atomic overlap with FcεRIα compared to E2_79 (omalizumab and FcεRIα =1183 Å^3 vs. E2_79 and FcεRIα =401



b

	KD nM	ID50 nM	Efficiency KD/ID50	Fold KD ID50/KD
Omalizumab	0.23	215000	1.07E-06	**934,782**
E2_79	5.05	15700	3.22E-04	**3,140**
bi53_79	12.00	184	6.53E-02	**15**

Figure 1. Structural correlates of disruptive inhibitor efficiency. (a) concentration dependence of IgE:FcεRIα dissociation measured by flow cytometry. (b) comparisons of binding (Kd) and disruptive dissociation (ID50) activities (c) structures of disruptive inhibitors bound to IgE.

Å^3). Since the E2_79 and omalizumab binding sites are substantially overlapping on the IgE-Fc, this large difference in steric overlap with FcεRIα stands out as a prominent structural feature that correlates with the relative disruptive activities of these inhibitors.

Our recent structural studies of the E2_79:E3_53:IgE-Fc complex show that the non-competitive E3_53 DARPin binds primarily to the IgE-Fc C□4 domains, anchoring the disruptive E2_79 DARPin to the complex and enhancing its efficiency of inhibition (Fig. 1c). We hypothesize that reengineering the E3_53 DARPin to select for high affinity, slow dissociating variants, would yield further improvements in bi53_79 activity. Studies to test this hypothesis are currently in progress.

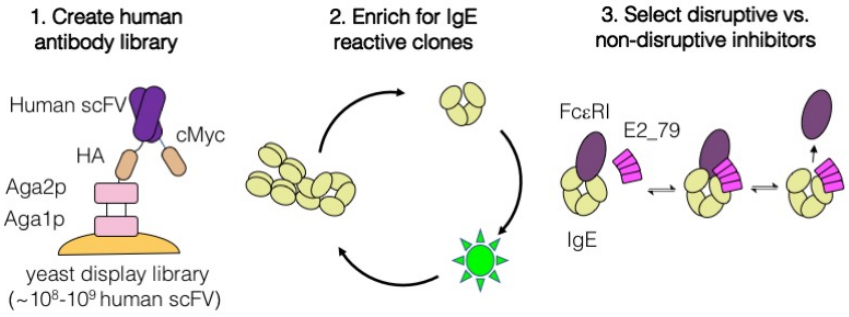


Figure 2. Selection of disruptive inhibitors from antibody libraries

Using yeast display antibody libraries to select for disruptive inhibitors. During the course of the original PRMRP award, we established the yeast surface display system[9] for the selection of novel antibodies that target and disrupt IgE receptor complexes (Fig. 2). In this approach, antibodies are displayed at the surface of yeast as single chain Fv constructs (scFvs) fused to the Aga2p anchoring protein[10,11]. We initially pursued a *de novo* strategy for identifying disruptive anti-IgE antibodies. We used a pre-existing human scFv library produced by the Wittrup laboratory[12], which has a diversity of ~10^9 antibodies. Using this scFv library, we selected a novel panel of ~20 anti-IgE antibodies and analyzed these for competition and potential disruption of IgE:FcεRI complexes. One of these antibodies with a potentially promising activity profile was further engineered to have higher binding affinity for IgE, using a PCR mutagenesis and library selection approach. In the course of these studies, we developed a more powerful, dual staining flow cytometry approach to facilitate screening for disruptive anti-IgE antibodies and established that our affinity matured anti-IgE antibody, as well as the parental clone, does not compete for receptor binding. However, this clone may

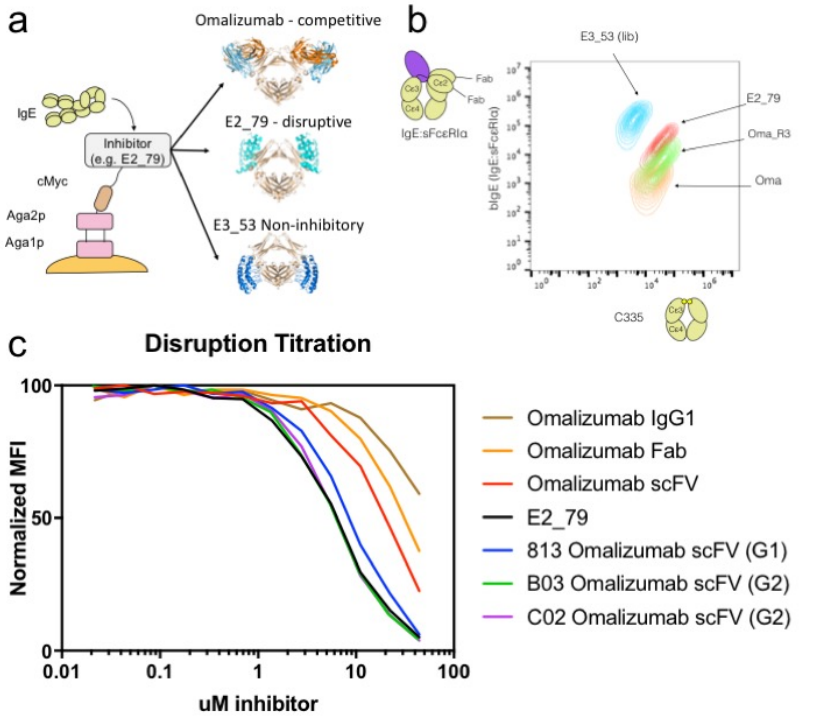


Figure 3. Selection of an omalizumab derivative with E2_79-like disruptive activity. (a) Shematic of yeast display constructs for control anti-IgE ligands (b) Example dual staining flow cytometry profile distinquishing three IgE ligands. (c) Titration profiles of engineered omalizumab variants with disruptive activity

prove useful as an anchoring anti-IgE for bivalent antibody constructs, similar to the anchoring role played by E3_53 in bi53_79. Based on these *de novo* anti-IgE selection studies and our structural studies of the omalizumab:IgE complex[8], we focused our efforts on re-engineering omalizumab to improve its poor disruptive activity. We reasoned that starting with a high affinity antibody for which we have structural information, provides a foundation for this re-engineering effort and a basis for understanding the underlying mechanisms.

Engineering omalizumab mutants with improved disruptive inhibitor activity. We generated yeast strains expressing omalizumab scFv, E2_79 and E3_53 to provide control profiles for competitive, disruptive and non-competitive IgE binders (Fig. 3a). These yeast strains were used to develop a dual staining protocol that could distinguish between these three classes of IgE binding proteins (Fig. 3b). E3_53 yeast bind IgE alone and in complex with FcεRI, while omalizumab shows preferential binding to free IgE (Fig. 3b). E2_79 shows intermediate activity between these two ligands, with an ability to bind IgE presented in complex with FcεRI that is representative of its disruptive inhibitory activity. We generated mutated libraries of omalizumab and carried out multiple stages of selection to produce yeast displayed mutants with staining profiles similar to E2_79. We have expressed a subset of these omalizumab variants and observe that theseexhibit disruptive inhibition activity that is similar to E2_79 (Fig. 3c). These are exciting results that demonstrate our ability to reengineer omalizumab to improve this activity and that provide a template for selecting other disruptive inhibitor candidates from other antibody-based libraries. We are currently focusing on understanding the omalizumab sequence modifications which yield the observed improvements in its activity. Overall, these data indicate that we were able to achieve our major Specific Aim 1 goals associated with the original proposal.

Specific Aim 2: Identification and validation of candidate small molecule IgE inhibitors from high throughput screening.

Major Task 2: Structure-function studies of small molecule lead compounds

In this aim of our original proposal, we sought to validate potential inhibitor 'hit' compounds identified through high-throughput screening. These hits proved difficult to validate, so we pursued additional screening using a fragment-based approach. We have obtained significant new data on fragment interactions with the IgE, which provide a very exciting opportunity to gain deeper insights into inhibiting a therapeutically important protein:protein interaction with small molecules and to potentially develop a lead compound inhibitor series with sufficient SAR data to support therapeutic development.

SPR-based high throughput screening of a fragment library identifies 200 hits that bind to the IgE-Fc. Fragment-based drug discovery (FBDD) is a widely accepted method for lead generation that is complementary to traditional high throughput screening[38-42]. FBDD has proven successful in generating lead and drug candidates, notably for challenging PPI targets[38,39,42]. Fragments are smaller than typical drug-like compounds and provide weakly binding hits, rather than high affinity inhibitors, that provide a starting point for synthesizing higher affinity analogs, preferably guided by structural information on the

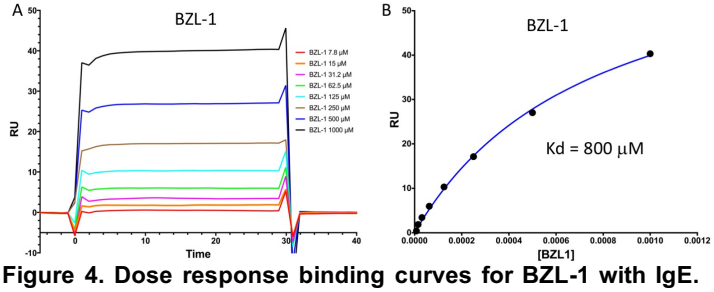


Figure 4. Dose response binding curves for BZL-1 with IgE. (A) Binding data of BZL-1 to IgE-Fc measured with Biacore T200. (B) The equilibrium affinity fit and K_D estimation for BZL-1 using BiacoreT200.

target:hit interaction.

We purchased a Stanford-designed fragment library of 5283 compounds from Maybridge and Life Chemicals to screen for binding to the IgE-Fc$_{3-4}$ fragment. We initially screened 960 compounds using a SensiQ Pioneer Fragment Edition SPR instrument, which identified 18 potential binding hits. We conducted follow-up screening of the entire library using a Biacore T200 instrument available in our PAN facility. We conducted dose-response binding experiments with a subset of the hits to assess quality and reproducibility of the binding interactions. One of our most promising hits, BZL-1, shows a binding affinity of ~800 µM (Fig. 4). The BZL-1 binding isotherm shows overall good behavior and is robust to repeated measurements randomizing the order of injection of the BZL-1 dilution series.

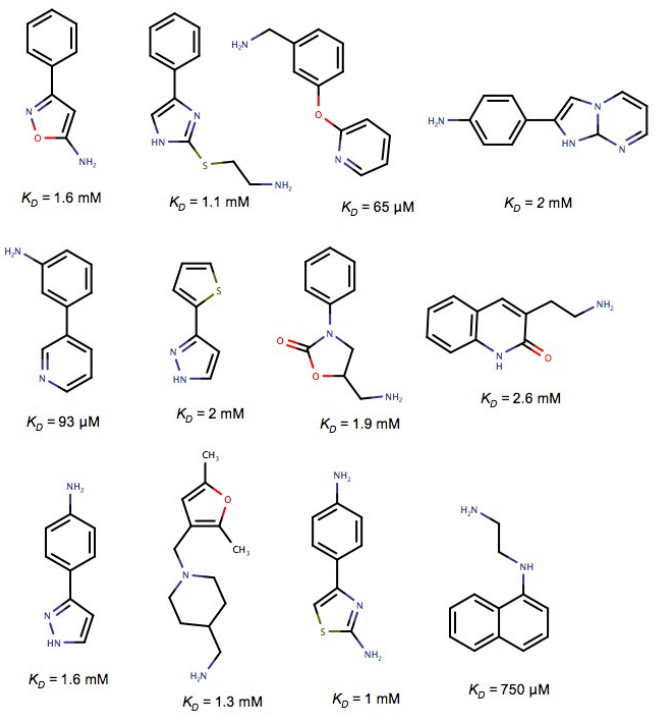


Figure 5. Chemical structures of representative hits identified from Biacore T200 screening

The Biacore T200 screen of the fragment library identified ~200 binding compounds for follow-up studies. We included BZL-1 as a positive control throughout this screening and this provided significant confidence in the data analysis and hit selection process because of its robust reproducibility. The ~200 hits can be clustered into different chemical classes (Fig. 5). While the affinity of the fragments is in the high micromolar to millimolar range, this is typical for initial hits in fragment-based screening and further modifications can lead to significant improvements in binding affinity[38]. One interesting observation that emerges from the fragment library screening relates to the potential to target the IgE-Fc with small molecules - fragment hit rates have been suggested to be one potential experimental indicator of druggability[43]. The observed hit rate for our entire screen is ~4%, which is in the range observed for a typical druggable target[43], suggesting that the IgE-Fc has an inherent ability to interact with small molecules that may make it a viable target for inhibitors. We hypothesize that this hit rate reflects inherent structural plasticity and adaptability in the IgE-Fc receptor binding loops that allows the IgE-Fc to bind multiple classes of small molecule scaffolds.

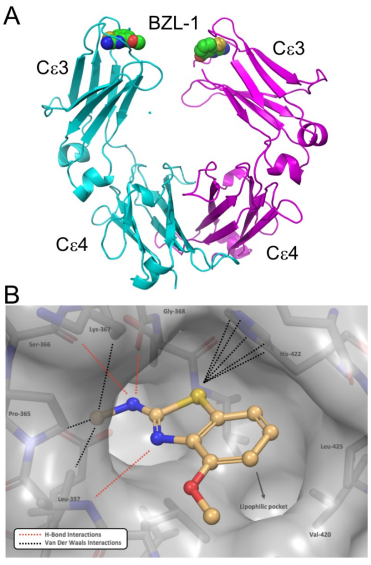


Figure 6. Overall structure of IgE-Fc:BZL-1 complex. a) IgE-Fc represented as ribbon diagram. BZL-1 represented as CPK models. b) A methylated analog of BZL-1 is shown in the binding site.

Crystal structure of the BZL-1 hit shows its binding to IgE-Fc Cε3 loops at the FcεRI-binding site. We determined the structure of BZL-1 in complex with the IgE-Fc (Fig. 6A). This represents the 'gold standard' for hit validation and development of a structure-guided analysis and optimization program[38,44]. BZL-1 binds to a pocket in the IgE-Fc Cε3 domain that is formed by loops involved in FcεRI binding. An overlay of the IgE-Fc:BZL-1

complex structure with IgE-Fc:FcεRI complex reveals steric conflicts that would block FcεRI binding. The IgE-Fc Cε3 loops surrounding the BZL-1 binding pocket adopt a different conformation, as compared to FcεRI-bound or apo-IgE structures, indicating the adaptive nature of this binding site.

BZL-1 belongs to a chemical class known as 1,3-benzothiazoles substituted with an amino group at C-2 and a methoxy group at the C4 position. The amino group at the C-2 position forms hydrogen bonds with the backbone carbonyl of Lys-367 and Gly-368. The nitrogen atom of the benzothiazole ring forms hydrogen bonds with the backbone NH of Ala-364, while the sulfur atom and the aromatic ring forms π-stacking interactions with the surrounding histidine residues (His-422 and His-424) and side chains of hydrophobic residues (Leu-363 and Leu-425). The methoxy group at the C-4 position makes hydrophobic contacts with the side chain of Val-336. The oxygen atom of the methoxy group also makes contact with the backbone NH of Leu-363 and Leu-364. Based on the SPR screening results, we found that analogs of BZL-1 present in the library that lack either the amino group or have a substitution of a bulky group at the C-2 position exhibit reduced binding to IgE, as indicated by a weak or absent SPR binding signal. The methoxy group at C4 contributes to binding significantly and its removal results in nearly 3-4-fold decrease in binding response units.

Preliminary SAR of BZL-1 improves its affinity and is consistent with the crystal structure. Based on the crystal structure of the IgE-BZL-1 complex, we identified exit vectors in BZL-1 that could accommodate various R groups to improve affinity. We also observed regions/exit vectors in BZL-1 that are detrimental for binding activity. A robust SAR model should include R groups that affect the activity positively and negatively in order to understand the structural requirements (steric and electronic) and assist in further rounds of optimization. Based on these hypotheses, we tested compounds that were commercially available in the direct SPR binding assay, with some leading to an improvement of affinity by ~5 fold, when compared to the starting fragment hit, BZL-1. Based on the binding affinity, it appears that the R1 position is sensitive to bulky R groups, especially linear and branching aliphatic chains. This preliminary SAR has led to clear improvement in the binding affinity (e.g. BZL-11, Kd = 170 μM; Fig. 7) starting from an initial hit BZL-1 with a Kd of ~1 mM. This provides an important foundation for further optimization and expansion of the BZL series by various medicinal chemistry strategies.

Small molecule fragments bind with low affinity and typically show poor initial activity. For many compounds solubility issues limit the ability to reach concentrations well above the Kd to effectively saturate the target. In addition, fragments are more likely to be promiscuous binders, which can further limit their specific activities in biological assays. It is not uncommon for initial, low affinity fragment hits to show weak or no inhibitory activity[38]. With BZL-1, we have observed partial inhibition (~15%) of IgE:FcεRI binding in a TR-FRET assay[45]. Improving the affinity in BZL analogs to low micromolar levels is needed to more rigorously test the inhibitory potential predicted by our structural observations.

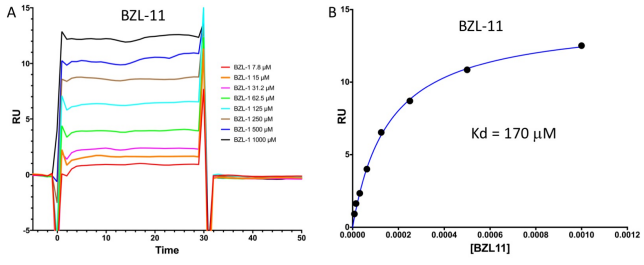


Figure 7. Binding of BZL-11 to IgE-Fc measured with the Biacore T200. The estimated Kd is ~170μM.

Analysis of other fragment hits identified from Biacore T200 and SensiQ screening. Apart from BZL-1, there are a number of other hits with different chemical scaffolds identified from our fragment-based library screen. The fragment hits were grouped to represent specific chemical classes (Fig. 5). Interestingly, for certain chemical classes

we observed a simple SAR trend emerging at the level of primary screening. For example, we identified additional thiazole compounds that showed a preference for an amino group on the thiazole ring. Substitution of the amino group with other groups affected binding as indicated by weaker SPR signals (response units) in the screening. In the case of aryl substituted pyrazoles, the location of the amino group on the aromatic ring appears to influence binding. We also found that certain fragment hits showed dissociation kinetics that more slowly reach the baseline signal, which may indicate higher affinity binding. The sensorgrams of these hits showed overall good binding behavior, with a fast association phase followed by an equilibrium phase and then a rapid dissociation phase. Analogs of these hits present in the library did not show any kinetic effects or showed weaker binding response. It is not uncommon for fragment hits to show some kinetics although full dose-response titration curves are needed to determine their affinity and binding profile. Most importantly, these screening hits provide a source of additional scaffolds that require further investigation.

Opportunities for training and professional development. Luke Pennington, a graduate student on the project, and Sarathy Karunan Partha, a research associate, both attended scientific meetings and presented their research results during the course of this award.

How were the results disseminated to communities of interest. The results from these studies were disseminated by publication (Pennington *et al*, *Nat. commun.*, 2016) and through presentations at conferences. TJ presented lectures based on these studies at meetings (IgE Regulation in Allergic Disease Workshop, NIH/NIAID, April, 2016; FASEB meeting IgE and Allergy, 50 Years and Onward, July, 2016; Type-2 Immunity Meeting, Bern December, 2017; GRC Food Allergy conference, January, 2018). Luke Pennington presented a posted as the 2016 FASEB meeting and has given oral presentations at Stanford in the MSTP and Immunology annual retreats. Sarathy Karunan Partha attended the Drug Discovery Chemistry Conference 2016 and presented a poster on our small molecule screening efforts. Additional manuscripts and patents are anticipated from this work.

4. IMPACT:

Impact on the principal discipline. Our major public contribution has been the determination of the omalizumab:IgE structure and development of an omalizumab-resistant IgE for both functional and potential therapeutic applications. These studies have garnered significant interest.

Impact on other disciplines. Nothing to report.

Impact on technology transfer. We patented our omalizumab-resistant IgE construct and are in discussions with a pharmaceutical company that has shown interest in using this technology in the development of novel anti-IgE-based therapeutics for food allergy.

Impact on society. Nothing to report.

5. CHANGES/PROBLEMS:

We experienced two significant challenges in our original proposed research plan which required developing alternative approaches. The first challenge was to develop a robust platform for selecting novel antibodies capable of disrupting IgE:FcεRI complexes. Based on our structural studies of the IgE:omalizumab complex, we realized that the proposed strategy of selecting antibodies based on epitope targeting would likely be insufficient to identify disruptive antibodies. We resolved this issue by establishing the yeast surface display system in the laboratory and by using a panel of control anti-IgE inhibitors to allow us to develop a robust

flow cytometry approach to selecting novel disruptive clones. Our second challenge was our inability to fully validate the small molecule hits that we had originally obtained from high throughput screening. In order to move this part of our project forward, we pursued a fragment-based ligand discovery approach, which has yielded very exciting results, including the demonstration that one of our fragments binds to the IgE-Fc by inducing a small molecule binding pocket at the IgE receptor binding site.

Anticipated problems or delays. Nothing to report

Changes in human subjects, vertebrate animals, biohazards and/or select agents. Because of our success in selecting novel anti-IgE antibodies using a yeast scFv display library, we did not conduct immunization experiments in mice.

6. PRODUCTS:

Publications. Pennington LF, Tarchevskaya S, Brigger D, KC, Eggel A, Jardetzky TS. Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. Nat Commun. 2016 May 19;7:11610. doi: 10.1038/ncomms11610. PubMed PMID: 27194387.

Website or other internet sites. Nothing to report.

Technologies or techniques. Nothing to report.

Inventions, patent applications and/or licenses.

"OMALIZUMAB RESISTANT IGE VARIANTS AND THEIR USE IN ANTI-IGE THERAPY," U.S. provisional application serial no. 62/217,709, filed on September 11, 2015

Other products. Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Individuals working on the project.

Name	Theodore Jardetzky
Project role	PI
Researcher Identifier	
Nearest person month worked	1.2 months
Contribution to project	Directed research
Funding support	

Name	Luke Pennington
Project role	Graduate student
Researcher Identifier	
Nearest person month worked	12 months
Contribution to project	Refined structure of the IgE:omalizumab complex; generated bivalent antibody constructs, generated omalizumab-resistant IgE, conducted yeast display experiments and analyzed disruptive activity of engineered anti-IgE
Funding support	Immunology training grant/ F30 NIH grant

Name	Svetlana Tarchevskaya
Project role	Research Associate
Researcher Identifier	
Nearest person month worked	12 months
Contribution to project	*Crystallized IgE:omalizumab complex, conducted small molecule inhibition experiments, crystallized ligelizumab:IgE complexes and solved/refined structure*
Funding support	
Name	Sarathy Karunan Partha
Project role	Research Associate
Researcher Identifier	
Nearest person month worked	12 months
Contribution to project	Conducted all studies on HTS lead compounds, conducted SPR-based fragment screening, obtained co-crystal structure of IgE-Fc with BZL-1 hit, conducted preliminary SAR on fragments analogs, developed alternative validation assays for small molecules
Funding support	

Changes in other support.

The following grants have ended:

1. NIH/NIAID R01 AI076183 Longnecker & Jardetzky (Co-PIs) 4/1/2008-3/31/2018
"Structural and Functional Studies of gp42 and HLA Class II in EBV Entry"; This proposal is part of a collaborative research program between Dr. Longnecker and Dr. Jardetzky to define the molecular mechanisms involved in Epstein-Barr virus (EBV) entry. The proposal will investigate the interaction of the EBV encoded gp42 with HLA class II and how this triggers fusion, allowing virus entry of B cells.

2. DoD PR130130 Jardetzky (PI) 9/1/2014-9/29/2017
"Novel IgE Inhibitors for the Treatment of Food Allergies"; In this proposal, we are examining a panel of anti-IgE antibodies that can inhibit IgE-receptor complexes. We propose in a second aim to follow up on a recent high throughput screen that we conducted to validate small molecule lead compounds for the treatment of allergic reactions.

3. NIH/NIAID R21 AI119480 Jardetzky, Longnecker, Zhou – co-PIs 7/1/2015-6/30/2017
"Structure and function of EBV protein complexes that trigger epithelial cell entry"
Here, we propose to study complexes of wild type and mutant gHgL with integrins that act as the entry receptor for EBV infection of epithelial cells.

4. NIH/NCI R01 CA117794 Jardetzky, PI; Longnecker, Co-PI 7/31/2012-5/31/2017
"Inhibitors of the Epstein-Barr Virus Entry Machinery"; The focus of this proposal is to develop lead inhibitors for known interaction sites in the EBV gp42 and gH/gL proteins that will block membrane fusion in B cells and to establish targets for inhibitor development for both B cell and epithelial cell entry.

Other organizations. Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS:
Nothing to report.

9. APPENDICES: n/a