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TITLE: STRUCTURE-BASED DESIGN OF INHIBITORS TO THE CYTOTOXIN RICIN

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4. TITLE AND SUBTITLE
STRUCTURE-BASED DESIGN OF INHIBITORS TO THE CYTOTOXIN RICIN

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14. ABSTRACT:
Ricin is a cytotoxin and a known bioterrorist weapon. The Army is pursuing anti-ricin vaccines, but plans to
develop an efficacious antidote to the toxin for cases where vaccination is not appropriate. The goal of this project was to use
the X-ray structure of ricin A chain (RTA) as a template for inhibitor design. Computer modeling and X-ray screening aid in the
design process. Inhibitors which bind to the RTA substrate specificity site have been identified. Several chemical platforms,
including 9-oxo-guanine and 9-deazaguanine, have been shown to bind in the RTA active site and act as a weak inhibitors.
However, efforts to derivatize and diversify the platforms via several strategies including triazole “click” chemistry have met with
unanticipated difficulties. None of the new compounds exhibits greatly improved inhibitory properties. A virtual screen of available
compounds suggests pyrimidines may provide a useful platform for future work.

15. SUBJECT TERMS
ricin; inhibitor design; X-ray structure; novel compounds

16. SECURITY CLASSIFICATION OF:
a. REPORT U
b. ABSTRACT U
c. THIS PAGE U

19a. NAME OF RESPONSIBLE PERSON
USAMRMC

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# Table of Contents

**Introduction** ........................................................................................................... 4  

**Body** ....................................................................................................................... 5  
  Task 1 ......................................................................................................................... 5  
  Task 2 ......................................................................................................................... 7  
  Task 3 ......................................................................................................................... 9  
  Task 4 ......................................................................................................................... 10  
  Task 5 ......................................................................................................................... 11  

**Key Research Accomplishments** ............................................................................. 11  

**Reportable Outcomes** .............................................................................................. 11  

**Conclusions** ............................................................................................................ 13  

**References** ............................................................................................................. 13  

**Appendix** ............................................................................................................... 15
INTRODUCTION

This contracted project was aimed at designing, synthesizing, and testing small molecule inhibitors of the cytotoxin ricin. Ricin is a class B biological agent which is known to be in the possession of terrorist groups (Loyd, 2001). Although not as menacing as infectious agents, ricin is of great concern because of the ease with which large amounts of semi pure material can be produced (Wellner et al, 1995). The Army is proceeding with vaccine development for key military personnel (Olson et al, 2004). However, wide spread vaccination of the military or civilian population is not practical or desirable, and so there is a need for an efficacious antidote. In addition to its utility such a compound could reduce social panic that might arise from a relatively minor terrorist incident. Our area of expertise is the rational design of inhibitors of enzymes like ricin A chain, RTA (Monzingo and Robertus, 1992; Yan et al, 1997; Miller et al, 2002). We elucidated the three-dimensional structure of ricin and used this model as a template to identify pteroic acid as a weak inhibitor of RTA activity. RTA binds a specific adenine base on the ribosome target and depurinates it (Endo et al, 1987); removal of the base inhibits at least 95% of protein synthesis activity (Ready et al, 1991). A picture of RTA with pteroic acid is shown in Figure 1. This represents the “open” form of RTA. In the apo protein the side chain of Tyr 80 closes over the adenine binding specificity pocket. Adenine, or the pterin of the inhibitor, moves the Tyr 80 aside to reach the specificity pocket.

The active site of RTA is an extensive depression that includes not only the deep specificity pocket, but a large surrounding cleft that can bind pendant groups attached to the specificity moiety. This active site was to be used in this program to identify, or help design, novel small molecules that can bind tightly and inactivate the toxin. These inhibitor compounds should also incorporate elements of drug design, including solubility, stability, and low toxicity. We have used computer searches to identify classes of inhibitors that act as “platform” molecules. These platforms have been modified and appended creating novel inhibitors for RTA. This particular project is a collaboration between structural biologists (Robertus group) and synthetic chemists (Kerwin group) to extend our previous research efforts on antidotes. It is a step-wise process, beginning with modest inhibitors, which are then sequentially improved after analysis, to produce ever more potent compounds; the program is scheduled to last three years. Our overall goal was to create a ricin inhibitor which is efficacious at inhibiting ricin intoxication of cultured cells, and itself was non-toxic and bioavailable.
The original Statement of Work (SOW) is as follows:

Task 1: Design improved specificity pocket (months 1 - 12)
   a. Prepare 9-oxaguaninine
   b. Prepare other related heterocycles

Task 2: Identify ligands for second ricin binding pocket (months 1 - 18)
   a. Use computer searches based on ricin structure
   b. Apply crystallographic screening of shape-diverse sets of commercial compounds

Task 3: Prepare tripartite inhibitors joining best specificity pocket and second pocket moieties with appropriate linkers (months 9-24).

Task 4: Use iterative crystallographic algorithm to refine tripartite inhibitors (months 12-36)
   a. Modify compound shape to fit enzyme contours
   b. Design compounds for maximum water solubility and biological uptake

Task 5: Test biological efficacy of inhibitors as ricin antidotes (months 1-36)
   a. Candidate inhibitors will be tested against ricin enzyme activity
   b. Ricin inhibitors will be tested for protective action in cultured human lung cells
   c. The most promising ricin antidotes will be sent to a commercial testing facility for initial human safety tests using a panel of enzyme and receptor assays.

However, financial strains caused the contract to be halted in the Summer of 2004 and restarted in the Fall with a reduced budget and the elimination of Tasks 5b and 5c.

ACCOMPLISHMENTS FOR PROJECT

TASK 1: Design and synthesize improved specificity pocket ligands

When the project began we had identified pteroic acid as a ricin A chain inhibitor (Yan et al, 1997). However, pteroic acid is poorly soluble and limits its utility as a platform for diversification. One of our first efforts centered on the 9-oxo-guanines as platforms. The preparation of the 8-methyl substituted 9-oxa-guanine derivative was originally carried out through cyclodehydration of the 5-acetamido-2-amino-4-hydroxypyrimidine (Figure 2). This compound was water soluble and inhibited RTA with an IC$_{50}$ ~ 400 M. As such it was a very promising lead inhibitor platform and a great deal of effort was expended in an attempt to diversify it. Over two years were spent trying to devise a useful synthetic strategy with a high yield and the capacity to construct a range of pendants at the 8 position. Table 1 indicates some of the experimental conditions that were attempted in order to synthesize the derivatives by cyclodehydration. Table 2 shows the results of an alternative synthetic approach involving direct annulation of the appropriate 4-amino-5-carboethoxyoxazoles. In spite of exploring a half dozen synthetic routes with a variety of chemical groups it eventually became clear that milder
conditions would be necessary in any successful approach to any pendants other than the 8-methyl group on the 9-oxo-guanine platform.

Another platform of interest was 9-deaza-guanine (9DG). Although not as water soluble as 9-oxo-guanine, this platform was more soluble than the pterins. The platform itself was observed to have an IC50 of 1.4 mM, and its binding was visualized by X-ray crystallography of the complex with RTA. To expand upon this initial success a number of synthetic strategies were undertaken. The most successful of these is indicated in Table 3. We observed that the simplest 9DG derivative, 7-methy-9DG, had an IC50 of 2.2 mM, and bound to the protein as predicted. We hoped that KeRCN-086, which mimics the pendant of pteroic acid, would be a much stronger inhibitor. KeRCN-086 was purified and tested as an RTA inhibitor. Despite the presence of the benzoate group, the compound was sparingly soluble and the IC50 could not be accurately measured.
In addition to the 9-deaza compounds we experimented with the related 7-deaza guanines (7DG). 7DG had an IC₅₀ of 2.8 mM, and was also observed by X-ray crystallography. It was rotated in the active site, around the long purine axis, compared with 9DG. This made it unclear where 7DG should be derivatized in order to avoid a clash of the pendant with the RTA protein. Since it was unclear if we should modify the platform at position 7 or 9 we procured an 8-methyl-7DG compound. It had an IC₅₀ of 2.1 mM suggesting that the small methyl group did not clash. Unfortunately we could never obtain a crystal structure of this complex to see clearly how it bound. Near the end of this project we procured a 4-(methylamino)benzoic acid derivative of 7DG (shown at the right) which had an IC₅₀ of 0.7 mM; it shows this platform has untapped potential.

Virtual Screening. Virtual screening uses powerful computer software to match the three dimensional structure of inhibitor candidates to the known active site of RTA. In principle this method may be able to identify novel platforms for inhibitor diversification. In the last year and a half of this project we acquired a parallel computer with 32 dual processors. We also acquired four pieces of virtual drug screening software, called ICM (Abagyan et al, 1994); GOLD (Jones et al, 1997; Verdonk et al, 2003), eHiTS (Zsoldos et al, 2006), and Surflex (Jain, 2003). Initially, we assessed these programs by docking a short list of known RTA inhibitors. These tests showed that the known inhibitor pteroic acid (PTA) was correctly docked, compared to the X-ray structure, by all four programs. Next, in a test using 1000 random compounds from the Sigma Aldrich data base (Irwin and Shoichet, 2005), PTA was ranked in the top 5% of predicted binding strengths by each program, suggesting that the programs were able to recognize the characteristics of a true inhibitor. However it is not clear that the rankings of these programs alone is definitive, and researchers judgment may be necessary to vet the computer “hit lists”. In particular, it is common that the programs give high scores to compounds that are so insoluble as to be impossible to assay.

Virtual screening has had mixed results for RTA. One program predicted a catechol, dobutamine, would be an RTA inhibitor. We purchased the compound and initially measured it as a potent (IC₅₀ ~ 1 µM) inhibitor. Attempts to grow crystalline complexes failed however, and we exhausted our dobutamine supply. When we reordered, the new shipment had a different color and did not inhibit RTA at all. We used NMR to show that the new shipment was indeed dobutamine; this suggested that the first shipment was contaminated with an unknown compound, or dobutamine product, that was a strong RTA inhibitor, but which is totally unknown to us. Recently however, virtual screens predicted that 2-amino-4,6-dihydroxy pyrimidine serves as a useful platform and we obtained several commercial derivative that are reasonable inhibitors. This work will be continued under other auspices.

We also used virtual screening to investigate possible binding modes of candidates for synthesis. That is, before committing efforts to create inhibitor candidates we employed virtual screening to see if such a compound had plausible binding modes, although as described above this is hardly definitive.

**TASK 2: Identify ligands for second ricin binding pocket**

As can be seen in Figure 1, the RTA active site is quite large. In addition to the specificity site that binds the substrate adenine (as well as pterin and guanine based inhibitors) there is a second pocket which can, in principle, accommodate large pendent groups. If a specific ligand...
could be identified for that site, and attached to the main platform, it could greatly increase the
binding affinity of the inhibitor. However, there is no clear assay to monitor binding at this
second site, since it is unclear it is involved in RTA enzyme activity. To explore this second site
we resorted to X-ray crystallography. The method involves soaking cocktails of “shape diverse”
organic molecules into the RTA crystals and seeing if anything binds in the extended RTA active
site (Nienaber et al, 2000). The composition of the first three shape diverse screens is shown in
Table 4 below. Note that the structures of the compounds within a library can be discriminated
from one another using X-ray crystallography; the members differ in size or in the number of
exocyclic moieties to give a distinct shape. We carried out a number of soaking/diffraction
experiments to search for second site ligands but they all failed. That is the difference Fourier
maps of the soaked crystals never revealed any significant binding. The major problem appears
to be that most of the candidates have poor solubility. We know that the Kd values for specific
active site molecules, like adenine, guanine, and pterins, are 1 -2 mM. It is likely the Kd for this
second site, when taken alone, is at least that high. The screening of shape diverse libraries
requires a good deal of organic solvent to dissolve the panel of compounds and this has
interfered with crystal screening, as it does with kinetic screening. It may be that computational
virtual screening will be more useful in identifying ligands for this second site; indeed docking
programs suggest that very nonpolar groups like naphthalene, fluorene, and acridan bind deep
in this second pocket.

<table>
<thead>
<tr>
<th>Shape diverse library #</th>
<th>Shape-diverse Compound Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KeAZB024 2-mercaptobenzimidazole 2,4,6-triaminopyrimidine 2-aminophenol</td>
</tr>
<tr>
<td>2</td>
<td>benzylamine 2-aminothiazoline 2-aminobenzimidazole Piperazine</td>
</tr>
</tbody>
</table>
**TASK 3:** Prepare tripartite inhibitors joining best specificity pocket and second pocket moieties with appropriate linkers.

A tripartite inhibitor involves a platform group that binds in the RTA specificity pocket, a pendant group that binds adventitiously at a remote site, and a chemical linker that joins the two and may also contribute to favorable binding. The rational design of such compounds was impeded by our failure to identify a chemical group that would bind specifically at a remote site. As a result, our efforts at tripartite synthesis became extensions of task 1, that is generating synthetic routes to modified platforms that contained “built in” linkers and pendant groups. Some of these were described above. In particular a great deal of effort was expended to diversify the 9-oxo-guanine and 9-deaza-guanine platforms.

Scheme 1 below shows a successful strategy to derivatize the 9-oxo-guanaine platform at position 8. Key to the success of this approach, which involves a three-step protocol to elaborate the six-membered pyrimidine ring, are the relatively mild conditions employed compared to previous routes (see Table 2). Compound 5c in the scheme contains a reactive azido group that can be further substituted by reduction to the amines, direct conversion to imines via the Staudinger reaction, or by “Click” chemistry involving coupling with terminal acetylenes to afford triazoles (Whiting et al, 2006). This versatile reaction class has been used in the creation of a number of commercial drug screening libraries. A number of elaborated molecules were synthesized, purified, and tested as RTA inhibitors.

**Scheme 2:** Synthesis of triazoles via 7-propargyl-9-deazaguanine.
The strategy for employing “click” chemistry with the 9-deaza-guanine platform is shown in Scheme 2. A number of derivative azides were “clicked” into this structure. Table 5 shows four elaborated molecules that virtual screening suggested could have plausible binding modes. All were synthesized, purified, characterized, and tested as RTA. Unfortunately, none showed significant inhibition.

Finally, we had noted that 9-oxo-3-thioxanthine (Figure 4) displayed modest activity against ricin with an IC\textsubscript{50} of \textasciitilde 4.8 mM. In order to determine if this activity could be increased by modification of the 3- or 8-substituents, additional analogs were prepared, as shown in Scheme 3. Cyclization of the 2-methyl or 2-iso-propyl oxazoles in base affords the 8-substituted 3-thio-9-oxo-xanthines. Alkylation of the 8-methyl derivative proceeded well with a variety of electrophiles to afford the S-alkylated derivatives. We once again took advantage of the versatility of Click chemistry to further elaborate the propargyl derivative to generate a range of triazoles. Based on our understanding of how guanines bind to the RTA specificity pocket, one would predict that modifications of the platform at the 3-thiol position would preclude “normal” purine binding. That is, groups attached there would clash with the active site residues that normally hydrogen bond to the exocyclic amine that is normally found at this position in substrates and other known inhibitors. However, some derivatives, like KeRCN120 shown in Figure 5 were modest inhibitors; this molecule showed an IC\textsubscript{50} of 1.6 mM. We were unable to obtain an X-ray structure of this complex and so we cannot define what must be a novel mode of binding by this class of compounds. It may be that it does not enter the specificity pocket at all, but binds to the “closed” form of the enzyme, as was seen by X-ray crystallography for the inhibitor 2,5-diamino-4,6-dihydroxypyrimidine.

![Figure 4: 3-thio-9-oxo-xanthine](image)

![Figure 5: RTA inhibitor KeRCN120](image)

**Table 5: Triazoles based on 9DG**

<table>
<thead>
<tr>
<th>Compound</th>
<th>ID</th>
<th>IC\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Compound Image" /></td>
<td>KeRCN109</td>
<td>\textasciitilde10 mM</td>
</tr>
<tr>
<td><img src="image" alt="Compound Image" /></td>
<td>KeRCN110</td>
<td>&gt;10 mM</td>
</tr>
<tr>
<td><img src="image" alt="Compound Image" /></td>
<td>KeRCN111</td>
<td>&gt;10 mM</td>
</tr>
<tr>
<td><img src="image" alt="Compound Image" /></td>
<td>KeRCN112</td>
<td>&gt;10 mM</td>
</tr>
</tbody>
</table>

**Task 4: Use iterative crystallographic algorithm to refine tripartite inhibitors**

Task 4 was never realized in this project. As described above we could not create true tripartite inhibitors that would serve as the base for a systematic, iterative modification based on observed IC\textsubscript{50} values correlated with structural contacts.
Task 5: Test biological efficacy of inhibitors as ricin antidotes

As described above the SOW was modified with a budget change to eliminate cell testing of inhibitors. In retrospect we did not identify inhibitor of sufficient potency to warrant such testing. We did use a cell free protein synthesis system to measure the strength of RTA inhibitors. During the course of this project we adapted our assay based on brine shrimp ribosomes to commercially available rabbit reticulocytes; we generally use RTA at 0.3 nM in our assays. To measure inhibitor strength we preincubate RTA with varying concentrations of inhibitor candidates and observe the effect on protein synthesis. Figure 7 shows the results for 8-methyl-9-oxo-guanine, perhaps the most potent platform molecule we found in this project. As discussed above, this platform was subjected to intensive derivatization efforts, although no modified compounds were superior to the base molecule.

A list of compounds known to inhibit RTA is shown in Table 6. The resolution of those complexes for which an X-ray structure is known are indicated in column 4 of the table.

KEY RESEARCH ACCOMPLISHMENTS

Perhaps the most important outcome of this project was the discovery that modified guanine compounds could serve as platforms for RTA inhibitor design. These include 8-oxo, 9-deaza, and 7-deaza guanine derivatives. These compounds are more soluble than the first RTA inhibitors which were based on pterins. A number of synthetic schemes were designed and tested. A variety of technical problems were overcome and useful procedures were achieved.

REPORTABLE OUTCOMES

A manuscript describing the new synthetic route to 9-oxoguanine derivatives is in preparation.
<table>
<thead>
<tr>
<th>2D Structure</th>
<th>Name</th>
<th>IC_{50}</th>
<th>(Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Pteric acid (PTA)</td>
<td>0.6</td>
<td>2.3</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Neopterin</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>4-(methylamino)benzoic 7DG</td>
<td>0.70</td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>8-ethylbenzoic acid-7DG</td>
<td>0.60</td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td>guanine</td>
<td>0.9</td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure" /></td>
<td>7-Me-9DG</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure" /></td>
<td>7-propyl-9-deazaguanine</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td><img src="image8.png" alt="Structure" /></td>
<td>9DG</td>
<td>1.4</td>
<td>2.6</td>
</tr>
<tr>
<td><img src="image9.png" alt="Structure" /></td>
<td>7DG</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td><img src="image10.png" alt="Structure" /></td>
<td>8-methyl-7DG</td>
<td>2.1</td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image11.png" alt="Structure" /></td>
<td>2-amino-6-hydroxy-8-mercaptopyrurate</td>
<td>0.56</td>
<td>N/A</td>
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<tr>
<td><img src="image12.png" alt="Structure" /></td>
<td>5-amino-2-methyl-6H-oxoioxazol (5,4d)pyrimidin-7-one (9OG)</td>
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<td>3.0</td>
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<tr>
<td><img src="image13.png" alt="Structure" /></td>
<td>KeRCN12 7</td>
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<td>N/A</td>
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<tr>
<td><img src="image14.png" alt="Structure" /></td>
<td>Thiazopyridazine</td>
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<td>N/A</td>
</tr>
<tr>
<td><img src="image15.png" alt="Structure" /></td>
<td>2,6-dihydroxypurine (xanthine)</td>
<td>3.6</td>
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<tr>
<td><img src="image16.png" alt="Structure" /></td>
<td>3-thio-9-oxo-xanthine</td>
<td>4.7</td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image17.png" alt="Structure" /></td>
<td>KeRCN12 0</td>
<td>1.6</td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image18.png" alt="Structure" /></td>
<td>2,5-diamino-4,6-dihydroxyisonicotinamide (DDP)</td>
<td>2.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>
CONCLUSIONS

The proposed inhibitor design project was far more difficult than originally envisioned. The active site of RTA is large and polar, evolved to accommodate a large number of weak interactions from a large RNA. Finding small molecules that make strong and specific interactions to compete with this large scale substrate binding is taxing. The 9DG platform molecule is itself a modest inhibitor, as are the 7-methyl and 7-propargyl groups. All can be seen in RTA complexes by X-ray. However, the “Click” chemistry-derived triazole constructs of 9-deaza guanine appear to be problematic - the large triazole group may prevent binding – and all of these analogs fail to inhibit. The 9-OG platform molecule is also an inhibitor, and synthetic difficulties in preparing more elaborate substituted 9-OG analogs have recently been overcome; however, none of these elaborated 9-OG inhibit better than the original platform. Even so, the diversity of subsites within the RTA target suggest that it should be possible to create tight binding inhibitors – it will simply require very skillful chemistry. We are also reasonable sanguine about the utility of in silico virtual screening. Tests recently completed suggest that the latest algorithms have merit, and may lead to identification of novel platform compounds and point to useful pendant groups as well.

“So what?”: The elaboration of two different platform inhibitors has as yet failed to lead to improved ricin inhibitors. The number and nature of the analogs prepared has been limited due to unforeseen problems with the synthetic routes and the very limited solubility of some of these elaborated compounds. Even after working around these problems, of the several new compounds that were prepared and tested, few were inhibitors and none were superior to the starting platform inhibitors. Our most recent approach has relied on “click” chemistry to link potential pendants to platforms. Although the chemistry is facile, the nature of the triazole linkers may not be optimum for ricin inhibition. None-the-less, it is essential to link larger pendants to the largely optimized platforms in order to improve binding by several logs. The route forward must carefully examine not only the nature of the pendant groups but also the linkers. In practical terms, this may require alternative platforms for which synthesis and solubility issues are more optimal for the evaluation of a large numbers of potential inhibitors.

REFERENCES


APPENDIX

List of Personnel Receiving Pay from the Research Effort

Jon D. Robertus, Principal Investigator
Sean Kerwin, Co-Principal Investigator
Stephen Ernst, Research Associate
Arthur Monzingo, Research Associate
Wen Tai Li, Research Fellow
Huda Suliman, Postdoctoral Fellow
Warren Hoe, Research Scientist Assistant
Jennifer Schleit, Research Scientist Assistant
Yan Bai, Graduate Research Assistant
Matthew Lluis, Graduate Research Assistant
Shuangluo Xia, Graduate Research Assistant
Cynthia Renteria, Undergraduate Research Assistant