Allergan (Research Grant or Support)Allergan (Research Grant or Support)Amplyx Pharmaceuticals (Research Grant or Support)Cidara Therapeutics (Research Grant or Support)Cidara Therapeutics (Research Grant or Support)Cipla Ltd. (Research Grant or Support)Cipla Ltd. (Research Grant or Support)Fox Chase Chemical Diversity Center (Research Grant or Support)GlaxoSmithKline (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Merck (Research Grant or Support)Merck (Research Grant or Support)Merck & Co, Inc. (Research Grant or Support)Merck & Co, Inc. (Research Grant or Support)Paratek Pharma, LLC (Research Grant or Support)Pfizer (Research Grant or Support)Qpex Biopharma (Research Grant or Support) Jill Lindley, Allergan (Research Grant or Support)Qpex Biopharma (Research Grant or Support) Timothy B. Doyle, Allergan (Research Grant or Support)Allergan (Research Grant or Support)Cipla Ltd. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Pfizer (Research Grant or Support)Qpex Biopharma (Research Grant or Support) Olga Lomovskaya, PhD, Qpex Biopharma (Employee)

167. A Phase 1b, Randomized, Double-blind, Placebo-controlled, Multiple-ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of DSTA4637S in Patients with *staphylococcus Aureus* Bacteremia Receiving Standard-of-care Antibiotics

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Session: O-32. Novel agents

Background: New treatment approaches for complicated *Staphylococcus aureus* bacteremia (SAB) are needed. DSTA4637S is a THIOMAB^{TM} antibody-antibiotic conjugate consisting of an engineered human IgG1 monoclonal antibody that binds to wall teichoic acid at the surface of *S. aureus*, a protease-cleavable linker, and a novel rifamycin class antibiotic, dmDNA31. This Phase 1b study assessed the safety, tolerability, and pharmacokinetics of DSTA4637S in patients with complicated SAB.

Methods: Multicenter, double-blind, placebo controlled, multiple-ascending dose clinical trial. Patients 18–79 years old with complicated SAB requiring at least 4 weeks of IV anti-staphylococcal standard-of-care (SOC) antibiotics were randomized to receive 4–6 doses of 15, 45, and 100 mg/kg IV DSTA4637S or placebo (6 active:2 placebo) every 7 days in combination with SOC antibiotics. Patients needed ≥ 1 blood culture positive for *S. aureus* collected within 120 hours prior to randomization. Patients were followed for 120 days after the end of treatment.

Results: Twenty-five patients with complicated SAB (bone & joint, n=14; endocarditis, n=5; other endovascular, n=5; pneumonia, n=1) were randomized and received 1–6 doses of study drug (19 active:6 placebo). Nine patients (36%) had MRSA. Ten patients completed ≥4 doses of DSTA4637S. The most common treatment-related adverse events were infusion-related reactions (IRRs) (5/19), and abnormal serum color (5/19)/skin discoloration (3/19 (due to dmDNA31). IRRs were not dose-dependent and were reversible with supportive care. Ten of 19 patients (40%) discontinued study drug (9 DSTA4637S,1 placebo); 4/19 (21%) due to IRR. DSTA4637S recipients showed no dose-related changes in laboratory values or vital signs vs. placebo. Observed exposures (C_{max} and AUC) were lower in patients immediately after dosing compared to a prior study in healthy volunteers; minimal accumulation occurred. No obvious trends in exploratory bacterial and inflammatory biomarkers were observed between treatment groups.

Conclusion: DSTA4637S in patients with complicated SAB demonstrated increased IRRs and decreased exposure compared to healthy volunteers, highlighting the importance of Phase I studies of novel treatments in infected SAB patients and not simply healthy controls.

Disclosures: Jeremy Lim, PharmD, Roche (Employee, Shareholder) Nicholas Lewin-Koh, PhD, Genentech (Employee) Tom Chu, MD, PhD, Genentech (Employee) Sharon M. Rymut, PhD, Genentech (Employee, Shareholder) Aklile Berhanu, PhD, Genentech, Inc. (Employee, Equity interest (Stock/Stock Options)) Montserrat Carrasco-Triguero, PhD, Genentech (Employee) Carrie C. Rosenberger, PhD, Genentech (Employee, Shareholder) Wouter L. Hazenbos, PhD, Genentech (Employee) Loren G. Miller, MD, MPH, genentech (Grant/Research Support) Vance G. Fowler, Jr., MD, MHS, Achaogen (Consultant)Actavis (Grant/Research Support)Advanced Liquid Logics (Grant/Research Support)Affinergy (Consultant, Research Grant or Support)Affinium (Consultant)Allergan (Grant/Research Support) Ampliphi Biosciences (Consultant)Basilea (Consultant, Research Grant or Support) Bayer (Consultant)C3J (Consultant)Cerexa (Consultant, Research Grant or Support) Contrafect (Consultant, Research Grant or Support)Cubist (Grant/Research Support) Debiopharm (Consultant)Destiny (Consultant)Durata (Consultant)Forest (Grant/Research Support)Genentech (Consultant, Research Grant or Support)Integrated Biotherapeutics (Consultant)Janssen (Consultant, Research Grant or Support)Karius (Grant/Research Support)Locus (Grant/Research Support)Medical Biosurfaces (Grant/Research Support)Medicines Co. (Consultant)Medimmune (Consultant, Research Grant or Support)Merck (Consultant, Research Grant or Support)NIH (Grant/Research Support)Novadigm (Consultant)Novartis (Consultant, Research Grant or Support)Pfizer (Grant/Research Support)Regeneron (Consultant, Research Grant or Support)Tetraphase (Consultant)Theravance (Consultant, Research Grant or Support)Trius (Consultant)xBiotech (Consultant) Jose M Miro, MD PhD, GENENTECH (Consultant, Scientific Research Study Investigator, Advisor or Review Panel member) Jessica A. Couch, PhD, Genentech (Employee, Shareholder) Melicent C. Peck, MD, PhD, Genentech (Employee)

168. Efficacy of the Novel gwt1 Inhibitor APX2039 in a Rabbit Model of *cryptococcus Meningitis*

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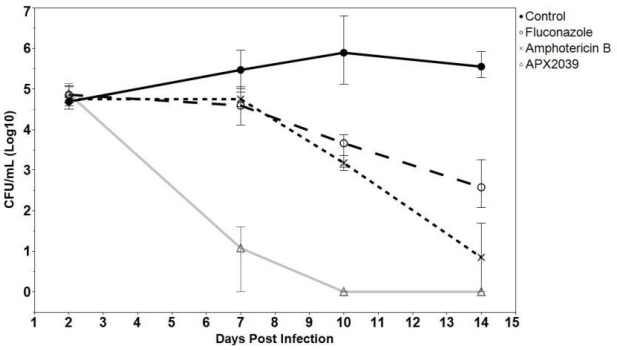
Session: O-32. Novel agents

Background: Cryptococcal meningitis (CM), caused primarily by *Cryptococcus neoformans*, is uniformly fatal if not treated. Treatment options are limited especially in resource-poor geographical regions, and mortality rates remain high despite current therapies. New oral treatment options are needed that demonstrate rapid reductions in CFU in CSF and brain tissue.

APX2039 is a novel inhibitor of the fungal Gwt1 enzyme, which catalyzes an early step in glycosylphosphatidyl inositol (GPI) anchor biosynthesis. It is highly active against both *C. neoformans* and *C. gattii* and has previously demonstrated significant efficacy in a mouse delayed-treatment model of CM.

CSF Fungal Burden in Rabbits



Methods: Male New Zealand White rabbits were inoculated with *C. neoformans* H99 (1.4×10^6 CFU) directly into the cisterna magna. Rabbits were immunosuppressed with cortisone acetate at 7.5 mg/kg (i.m.), starting on Day -1 relative to inoculation and then administered drug daily throughout the 14-day experimental period. Treatment was initiated on Day 2 postinfection and continued through Day 14 consisting of: 50 mg/kg APX2039 PO (BID), 80 mg/kg fluconazole (FLU) PO (QD), c) 1 mg/kg amphotericin B deoxycholate (AMB) IV (QD); and vehicle control. CSF was removed via an intracisternal tap on Days 2, 7, 10 and 14 post-infection and CFU/ml was assessed. Animals were sacrificed on Day 14 and CFU/g brain tissue was assessed.

Results: APX2039 demonstrated rapid reduction in CFU in both CSF and brain tissue. The range in CFU values in rabbit CSF is shown (Figure). Reductions in CFU were statistically different from the control group for all treatment groups. APX2039 was also different from both FLU and AMB and resulted in sterilization in CSF by Day 10. Brain harvested on Day 14 demonstrated a reduction in CFU/g tissue vs control of 1.8 $\log_{10}$ and 3.4 $\log_{10}$ for FLU and AMB, respectively, while a > 6 $\log_{10}$ reduction (tissue sterilization) was observed for APX2039.

Conclusion: APX2039 demonstrated potent efficacy in a rabbit model of CM. The more rapid clearance in CSF than either AMB or FLU, as well as > 6 $\log_{10}$ reduction in brain CFU highlights the unique properties of this drug, warranting further investigation of this molecule for the treatment of CM.

Disclosures: **Karen J. Shaw, PhD**, **Amplyx** (Consultant)**Forge Therapeutics** (Consultant) **Charles D. Giamberardino, Jr., MR**, **Box** (Shareholder) **John R. Perfect, MD**, **amplyx** (Grant/Research Support)**astellas** (Grant/Research Support)**astellas** (Grant/Research Support)

169. AT-752, an Oral Guanosine Nucleotide Prodrug, Exhibits Potent *in Vitro* Activity Against Flaviviruses and Prevents Disease Progression in a Dengue Mouse Model

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Session: O-32. Novel agents

Background: The increasing global prevalence of human Dengue virus infection and the potential for life-threatening sequelae highlight the significance of this unmet medical need. Here we report the potent *in vitro* activity of AT-281, the free base form of AT-752, against Dengue virus and other flaviviruses and the *in vivo* efficacy of AT-752 in a mouse model of Dengue viral disease.

Methods: Antiviral activities of serial dilutions of AT-281 were evaluated in infected Huh-7 cells. Effective concentrations of AT-281 required to inhibit virus yield reduction by 90% (EC_{90}) and to prevent cytopathic effect by 50% (EC_{50}) were