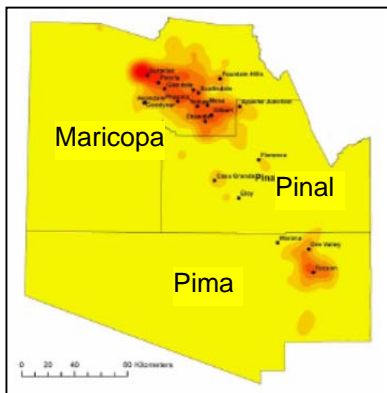
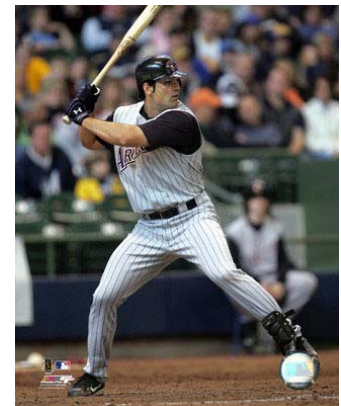


The Search for the Cure for Valley Fever Nikkomycin Z Development at the University of Arizona

May, 2016



Each year, Valley Fever (coccidioidomycosis) causes 50,000 new illnesses. More than half of these fungal infections occur in Maricopa, Pinal, and Pima counties (the “Valley Fever Corridor”). The Arizona Department of Health Services found that in 2007 hospital costs alone were \$86 million. However, patients like Conor Jackson of the Arizona Diamondbacks, who missed most of the 2009 major league baseball season because of his Valley Fever condition, would not have been included in that statistic since his was considered the more mild form of illness. Current therapies for this disease are partially effective but do

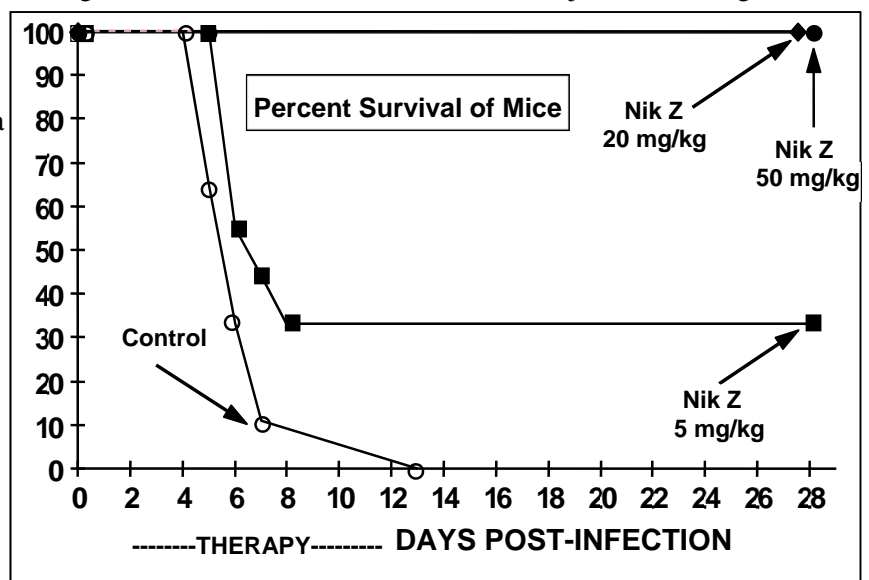


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not eradicate the fungus from the body. Thus, many patients who are treated have their disease return when drug treatment is stopped. The BIO5 Institute and the College of Medicine at the University of Arizona are trying to change this situation.

Nikkomycin Z: A possible Valley Fever cure

Nikkomycin Z (NikZ) was discovered by a major pharmaceutical company in the 1970s. This drug is made by a bacteria and acts by blocking the enzyme that makes “chitin,” an important building block in fungal cell walls. People and animals do not make chitin and the enzyme target of NikZ is absent. Therefore, NikZ might have little or no toxicity for the patient. In the 1980s, experiments in mice demonstrated that NikZ was a very effective treatment for Valley Fever and might cure it. An actual cure would be a major breakthrough. A small pharmaceutical company started clinical development of NikZ but this activity stopped in 2000 when the company failed. For the next five years, a small foundation in California tried to find a pharmaceutical company to continue development of NikZ but was unsuccessful. The consensus was that the problem of Valley Fever – and therefore the market for drugs to treat it – was “too small” and profits not sufficiently large. At that point, the Valley Fever Center for Excellence at the University of Arizona assumed sponsorship of the project and restarted NikZ’s development.



Nikkomycin Z development at the University of Arizona since 2005.

When the UA first became involved, less than a dozen individuals had received a single dose each of NikZ. The next step was to give new volunteers multiple doses and see if this was well tolerated and safe. A modest amount of NikZ powder from the original test sequence was available to use for the continuing safety trial without manufacturing more. The UA now has completed a study of three dozen volunteers who received doses ranging from 50 mg per day to 750 mg three times per day for two weeks. The analysis is not complete but no adverse events were seen. This recent testing allowed drug levels to be measured in the blood and urine of these subjects, providing important information about absorption of the drug and how it leaves the body.

In further mouse studies, researchers are learning more precisely what doses of drug provide optimal treatment for experimental infections and what drug levels in the mice are associated with this degree of treatment success. Comparing this information to the results in the human volunteer study should provide a firm basis for designing future studies to select reasonable doses to effectively treat patients.

The Valley Fever Center needs to make more NikZ before it can continue with future studies. The UA has a new manufacturing process to make NikZ at a lower cost. Central to this, a UA biochemist succeeded in deleting a gene in the NikZ-producing bacteria. This resulted in the elimination of a major impurity, making purification of NikZ simpler.

Who's paying for the development of nikkomycin Z?

Drug development is expensive. The work has been supported by several research grants from the National Institutes of Health (NIH), the Office of Orphan Product Development of the Food and Drug Administration (FDA), and seed grants from the Critical Path Institute and the BIO5 Institute. The Center also received a series of gifts from the Manhattan-based JT Tai & Company Foundation, now totaling \$3.0 million. A small business (Valley Fever Solutions, Inc.) was formed to support this project and has succeeded in bringing nearly \$6 million in NIH small-business grants to Arizona for

NikZ development. All told, approximately \$12 million has been found to move NikZ forward.

Until more NikZ is manufactured, clinical trials cannot proceed. While the NIH has been very supportive of our efforts, ultimately, additional investment will be needed to make NikZ clinically available for patients with Valley Fever. Potential investors have expressed interest for some time but have been waiting for some technical and scientific milestones. Recent progress has brought a closer look by some new potential investors, although no firm commitments have been made.

Summary

Valley Fever is considered an "orphan disease" because at any one time fewer than 200,000 people in the United States are sick from this infection. However, about two-thirds of the infections are in Arizona and most of those in Maricopa County. The Valley Fever Center for Excellence at the University of Arizona is the only academic research institution in the world focused on this disease. Taking the lead in developing a possible Valley Fever cure is very much within its mission. Center efforts have capitalized on the UA's academic strength in biochemistry, proteomics, genetics, pharmacology and medicine. As a result, a drug that otherwise has been ignored by pharmaceutical companies now is in active development. UA researchers hope that this, along with other research into improved diagnostics and ultimately a preventative vaccine, ultimately will be a boon to public health across the Southwest and most especially in Arizona.

For further information, contact:

John N. Galgiani, MD

Director, Valley Fever Center for Excellence

Tel: (520) 626-4968

Fax: (520) 626-4971

Email: spherule@u.arizona.edu Website: www.vfce.arizona.edu