Innovations

Basilea Pharmaceutica AG
Mining a Rich Inheritance

Given that Basilea only opened its doors in October 2000, you may not yet be familiar with their name and their mission to develop novel anti-infective and dermatological therapies. But this Basel, Switzerland-based, Research and Development-focused company has a powerhouse of a parent in F. Hoffmann-La Roche Ltd. According to Basilea’s CEO, Dr. Günther Kinast, the company’s objective is to join the “Champions League” of the biotech and pharmaceutical world. Fortunately, the company has a jump start on this goal: in only two years it has progressed to produce a steady flow of innovative compounds and already has two compounds in phase II testing.

In 1999, when Roche made its strategic decision to refocus its own R&D activities away from anti-infectives and dermatologicals, rather than scrap or license away all the technology that its scientists had accrued to its competitors, it decided to create a new, distinct company (Basilea), to which it assigned pertinent drug candidates and all relevant intellectual property. Consequently, Basilea’s 110 employees have one goal: to develop and discover new antimicrobial and dermatological therapeutics. Aside from the management team, almost everyone at Basilea is involved in research and clinical development projects that are driven by mining the assets inherited from Roche. It is noteworthy that although Basilea is an independent company, Roche still holds 49% minority ownership and retains an opt-in right at the end of phase II development on seven of the compounds currently in the Basilea pipeline.

Dermatology Compounds in the Lead

When the company was formed, most of the R&D staff came from Roche. “So did five development compounds that we’re pursuing now,” says Chief Development Officer Anthony Man, MD. “Because of the assets we were born with, our current focus and core competency is in the treatment of infectious diseases and dermatological diseases.” “Our two most advanced products now are in the dermatology area,” adds Discovery Program Head Malcolm Page, PhD, himself a ten year Roche veteran. BAL 4079, or altretinoin, is an oral vitamin A derivative developed for the treatment of chronic hand eczema, which is now in phase II trials. Man describes this drug as the lead agent, by far, of all compounds in development.

“BAL 4079 is a natural compound, and it’s important to realize retinoids are a very heterogeneous group,” explains Man. Further, in the field of dermatology there is a record of retinoid efficacy in various disease types, including acne, psoriasis, and eczema. “But it’s not possible to predict preclinically which disease may be helped by which retinoid.” He adds it is equally difficult to extrapolate which drug will be most effective as an oral systemic drug or as a topical agent. “The receptor subtype to which a retinoid binds likely determines, to some extent, the diseases for which it may be effective in treating,” Man continues. “BAL 4079 binds to the both the RAR and RXR families of retinoid receptors.” This suggests that this agent may have broader efficacy than other retinoids. It is hypothesized that BAL 4079 may exert its effect on eczema by decreasing Th1 cell activity and inhibiting the release of cytokines. The published results of a 38-person open-label pilot trial for chronic hand eczema indicated that 34 participants had a response to the medication, ranging from good to very good, with only two patients exhibiting no response. The side effects were mild, with 29% of participants experiencing cheilitis (dryness and cracking) and 11% each having headache or flush. Other Th1-cell-mediated diseases like multiple sclerosis, lupus, Crohn’s Disease, and rheumatoid arthritis may also be considered for clinical investigation, but Man is quick to add that BAL 4079 has not been tested for effectiveness in these, or other, diseases.

Basilea is targeting a patient population with chronic hand eczema who do not respond to conventional topical therapy such as steroids and emollients. “There is no good alternative for that particular patient,” says Man. Should BAL 4079 pass its clinical and regulatory hurdles, it will join the ranks of other retinoids including tretinoin (Retin-A), isotretinoin (Accutane), and actitretin (Soriatane). The current phase II study is a randomized, double-blind, placebo-controlled 300-person trial comparing several doses. “We should have the results out by the end of 2002,” says Man.

The company’s other promising dermatology therapeutic is BAL 2299, a vitamin D derivative in early phase II tests for psoriasis. In this case, the clinical trials have advanced further. “We’ve identified an appropriate dose for the BAL 2299 phase II study and we’re in exploratory clinical testing now with that drug,” says Man. For mild psoriasis, a number of topical psoriasis medications are available including vitamin D3 derivatives. At the severe end of the spectrum for the disease, arthritis and other complications re-
quire more extreme and aggressive treatment with immunosuppressants or biological agents such as monoclonal antibodies. "We're positioning BAL 2299 somewhere in between the gap between the topical applications and these 'high-tech' therapies. We are hoping to have a psoriasis compound that would satisfy the needs of patients for whom topical treatments are either ineffective or inconvenient, but for whom more high-tech solutions often involving immunosuppression are a bit too heavy handed."

**Broad-Spectrum Antibiotic in Its Sights**

In addition to the dermatological therapies, Basilea has a broad-spectrum IV cephalosporin prodrug, BAL 5788, just about to enter phase II for dose confirmation. Excitingly, this drug has activity against both gram-positive and gram-negative bacteria. "Clinically, some of the most worrisome pathogens are the gram-positive cocci—staphylococci, enterococci, streptococci—which are causing big problems at the moment," says Page, who was on the drug's development team at Roche. He explains, "One key advantage of the BAL 5788 drug is that it combines well-established features of a β-lactam antibiotic agent with very good activity against meticillin-resistant *Staphylococcus aureus*, or MRSA." MRSA is a major problem in many hospitals throughout the world, and many facilities are now resorting to their last line of defense against it, principally with vancomycin. "There is a severe shortage of drugs available for effective treatment of MRSA infections," according to Page.

BAL 5788 has also exhibited activity against penicillin-resistant *Streptococcus pneumonia*, viridans streptococci, and coagulase-negative staphylococci such as *Staphylococcus epidermidis*. "Staphylococcus is the most common cause of infection in humans," says Man. "You'll find the infections both in the out-patient community and hospital settings." It is also commonly involved in wound (skin and soft tissue) infections. Streptococcal infections are commonly acquired as lower respiratory infections. "In fact, *Streptococcus pneumonia* is the lead cause of community-acquired bacterial pneumonnia" according to Man, "and streptococci infections are also involved in skin and soft tissue infections in both the hospital and community." While staphylococci and streptococci are part of the normal indigenous bacterial flora, under certain conditions they will overgrow and cause disease. "They are notoriously resistant to most antibiotics," says Man, "but vancomycin is effective in some cases of resistant staph infection."

However, with the increasing prevalence of antibiotic-resistant strains of bacteria and the resultant increasing use of vancomycin, vancomycin resistance has developed in certain organisms, particularly in Europe and Japan, but to some extent in North America too. "However, we do not believe that BAL 5788 should be limited to glycopeptide-resistant gram-positive bacteria, because its in vitro profile also extends to gram-negative organisms," says Man. Neither vancomycin nor some of the newer drugs such as linezolid or quinupristin/dalfopristin have activity against gram-negative organisms.

**Antifungals Complete the Core Program**

In the antifungal arena, Basilea is developing BAL 8557, a water-soluble azole, which is being produced both as an oral and IV therapy. "This gives the clinician a choice for applications," says Page, "depending on the type and site of infection." BAL 8557 will primarily be targeted for treatment of serious invasive systemic fungal infections. "You can start patients who are seriously ill on the IV form, then switch to the oral once the infection is better controlled," adds Man. BAL 8557 is just about to enter phase I testing. The other antifungal effort is a preclinical project focused on inhibition of glucan synthase. "We have a number of molecules from this field," he says, "and we'll probably decide by the end of the year how to proceed with this group of compounds."

**Natural Products Library and Chemistry Automation**

When Basilea was formed, it also inherited a "natural products strain collection," a microbe library of 120,000 organisms, each with the potential or proven ability to synthesize antibiotics or other therapeutic agents. "We have access to several hundreds of thousands of synthetic compounds for screening in addition to the natural product library," explains Man.

In partnership with its parallel chemistry group, and also with a head start from Roche, Basilea is developing new chemistry automation that is more flexible than current conventional combinatorial chemistry. "We do targeted chemistry using information from screening our compound libraries and our extensive knowledge of the crystal structures of new targets to design new ligands, and then make small focused libraries rather than the large, homogeneous sets that have been the fashion with combinatorial chemistry," explains Page.

While Basilea will have plenty to do with its treasure from Roche for the foreseeable future, they are actively interested in collaborations with other companies for licensing-in opportunities. While no such agreements have been announced publicly, talks are in the works with several prospective partners. "In comparison with typical start-up companies, we have a big development product portfolio," says Man. "Though we're always interested in new opportunities, we certainly have enough going on in-house to keep us busy."

*Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.

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