What's your poison?

How do you milk a spider? "Very gently", says Dr Rose Roeloffs, a Research Scientist at NPS Pharmaceuticals (Salt Lake City, UT, USA; Figure 1). Roeloffs should know; she collects venom from spiders and scorpions from around the world. The collection has at times numbered up to 15,000 individual animals (Figure 2).

NPS was founded on the basis of research into the mechanism of action of venoms, derived mainly from spiders and scorpions. This unusual approach led to the discovery of novel compounds with potential for the treatment of stroke. But now the company is at a crossroads. Their first drug candidates, compounds that act on a novel class of calcium ion receptors, are in development for the treatment of osteoporosis and hyperparathyroidism. However, these compounds did not come out of the venom work, and company officials are discussing the future of the novel program.

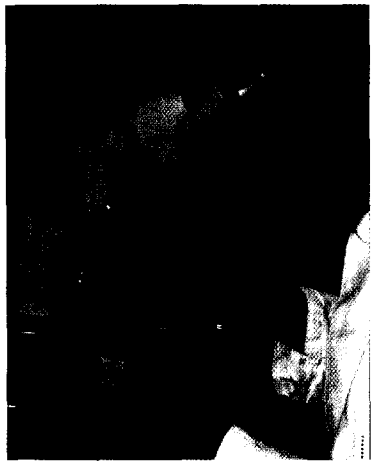

Figure 1. *Dr Rose Roeloffs 'milking spiders' at NPS Pharmaceuticals.*

NPS origins

The company was founded in 1986 by Hunter Jackson and Thomas Parks, both professors in the medical school at the University of Utah with an interest in using insect venoms to dissect neurophysiology. They were particularly intrigued by the manner in which certain venoms altered the transport of glutamate in brain slices. From preliminary studies using just a few venoms, Jackson and Parks realized that the venoms contained interesting compounds that might be useful in treating stroke victims. "Glutamate is a major neurotransmitter in insects, so it's not unreasonable to find that the venoms of animals that feed on insects contain potent glutamate antagonists capable of paralyzing an insect by blocking glutamate receptors," explained David Clark, Director of Corporate Communications; "and in humans, glutamate is an important component in the neural damage caused by ischemic stroke, which results in an overabundance of glutamate followed by the opening of calcium channels that, if left unchecked, leads to massive depolarization and neuronal cell death." The two neuroscientists discovered that some components of the spider venoms can modulate the effects of glutamate, thus providing a potential protective effect for stroke victims.

It soon became clear to Jackson and Parks that it would require a commercial company to collect a wide array of venoms and pursue a serious effort in drug discovery; the result was the formation of NPS Pharmaceuticals. Today, Jackson is CEO, President and Chairman; Parks is a member of the Board of Directors and the George and Lorna Winder Professor of Neuroscience and Chairman of the Department of Neurobiology and Anatomy at the University of Utah School of Medicine (Salt Lake City, UT, USA); and NPS is a public company with approximately $65 million in the bank. NPS hopes to commence clinical trials shortly on a drug for the treatment of stroke; according to Clark, the drug "is not a natural product but it does have its roots in the early work with venoms."

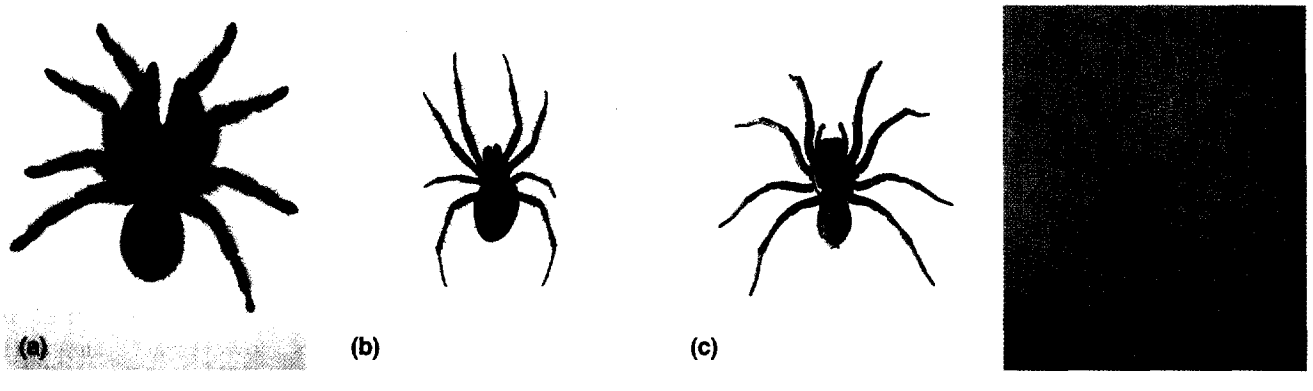

Figure 2. *Some members from the NPS collection. (a) Chilean rose hair tarantula; (b)* Neoscona *sp.; (c)* Lycosa grande*; (d)* Nephila *sp. (from Fiji).*

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Unconventional husbandry

NPS scientists maintain, breed and 'milk' spiders (from tiny specimens to the large hairy tarantulas), scorpions and centipedes. An inventory of approximately 100 different venoms is maintained for investigation, and is quite likely to be the largest collection in the world according to Roeloffs.

To collect or 'milk' the venom, a spider is first relaxed with a brief blast of carbon dioxide. A small electrode is attached near to the fangs, and a slight electric shock is used to stimulate the release of a droplet of venom, usually no more than a few µl and sometimes less than 1 µl. The fluid is collected in a tiny capillary tube and combined with the product of many repeated milkings from the same individual or others of the same species. Roeloffs says that in some cases "the milking procedure has been repeated up to 10,000 times to get enough material for analysis." For a complete analysis, which includes determining its effect in several bioassays, isolation of the active component, and elucidation of its molecular structure, 1 ml of a venom is often needed.

The venoms often represent a mixture of up to 100 peptides, proteins or polyamine-like compounds (Figure 3), but modern microseparation techniques allow each component to be investigated individually. Based upon their extensive experience with the venoms, NPS views the venom components today not necessarily as potential therapeutic substances, but as compounds that may point the way to receptors on mammalian cells that have never been identified or well characterized. They believe the venoms to be invaluable tools for the identification of novel drug targets.

New direction?

However, NPS has grown considerably, and today it is much like any small pharmaceutical company using all available means to identify new drug leads, including screening of compound libraries, combinatorial chemistry and extensive efforts in medicinal chemistry. According to Dr Derek Hook, Director of Drug Discovery, the company's research took a new direction about five years ago when Dr Edward Nemeth, now Vice President of Research, was recruited from Case Western Reserve University. Nemeth brought to the company his expertise in calcium ion receptors and was instrumental in developing a collaboration with Drs Edward Brown and Steven Hebert at Brigham and Women's Hospital (Boston, MA, USA) on the isolation and characterization of calcium ion receptors. Together they discovered a cell surface receptor on parathyroid cells that responds to the changes in extracellular calcium ion levels, and through traditional screening of defined chemical libraries, found agonists that mimic the effect of calcium ions on the receptor.

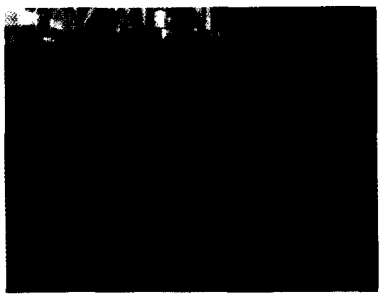

Figure 3. *HPLC chromatogram of spider venom; each peak corresponds to a different component.*

Calcimimetics

The calcium receptor was the first identified for an inorganic ion and plays an important role in regulating the levels of circulating parathyroid hormone and serum calcium levels. Exploitation of the calcium ion receptor for drug discovery is clearly the major accomplishment of the company to date. The collaboration with Brigham and Women's Hospital continues. The focus is on the identification of other ion receptors that NPS scientists believe may exist and the characterization of calcium ion receptors on a variety of other tissues.

NPS's lead calcium agonist, R568, has been through two Phase I and two Phase I/II clinical trials. Together with similar 'calcimimetics', it has been licensed for the treatment of hyperparathyroidism to the pharmaceutical division of the Kirin Brewery Company (Tokyo, Japan) for marketing in Japan, China, Korea and Taiwan, and to Amgen (Thousand Oaks, CA, USA) for all other countries. Both Amgen and Kirin are continuing clinical trials. If it makes it to market, R568 will be the first specific agent for the treatment of hyperparathyroid patients; worldwide annual sales have been estimated at approximately $1 billion by Salomon Brothers' analyst Meirav Chovav.

Through a collaboration with SmithKline Beecham (Philadelphia, PA, USA), NPS has also discovered orally active compounds that may promote the regrowth of bone in the treatment of osteoporosis. SKB has worldwide rights to market the compounds, which are currently in development.

The discovery of calcimimetic drugs has already done much for NPS's bottom line. In May of 1996 a secondary stock offering brought in $45 million, some 76% more than the company initially expected. Only two years before, the initial public offering was completed with only 2 million shares sold at $5.50 each, with its stock soon dropping to $3.75 a share. Much of the turnaround is credited to enthusiasm over the calcimimetic drugs. In addition to the stock offering, NPS has received considerable funding in licensing fees for the calcimimetic drugs: $5 million from Kirin Pharmaceutical Division plus a $2 million milestone payment, and $10 million from Amgen who also purchased $7.5 million of NPS stock.

Future for venom program

Because of the success of the calcimimetics, much of the future drug discovery research at NPS will focus on calcium receptors and other novel receptors. However, according to Hook, there is now an ongoing discussion about the future of the venom program as a tool for identifying new targets rather than therapeutic compounds. One possibility, says Hook, is that the

company will put together a screening kit that it will offer to academic laboratories in an attempt to identify new drug targets. The kit would contain approximately 25 spider and scorpion venoms that would be made available on a coded basis to an outside laboratory for screening in its bioassays. If something interesting was found, NPS would ask the right of first refusal to collaborate on the project and to develop any drug leads that might arise.

Another possibility is to use the venom program as a basis to collaborate with other pharmaceutical companies or to develop collaborative relationships with agricultural companies to test the venoms as possible biopesticides. These are not new ideas; in the past NPS had collaborative relationships with Pfizer (New York, NY, USA) and FMC (Princeton, NJ, USA) to search for novel compounds including pesticides.

Finally, as in any corporate environment, there is always the possibility that a program might be discontinued so that its resources can be redirected. "The venom program is valuable as a tool to identify new targets, and new activities are frequently discovered by those studying venoms. Our dilemma at the moment is that the spider program utilizes a significant portion of our resources," says Hook. "We are in the position where we would like to partner this program with an institution that is more directed in this area of research." So, spider, scorpion, centipede venoms anyone?

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Society for Biomolecular Screening – origin and future role

In the late 1980s, high-throughput screening (HTS), which was a new science, drew upon expertise from all other disciplines without therapeutic area boundaries. Although it began as the means of identifying starting points, screening has quickly become the focal point of drug discovery by identifying lead molecules for the start of synthetic chemistry programs. Scientists involved in HTS belong to a variety of disciplines including biochemistry, microbiology, molecular biology, chemistry, pharmacology, cell biology, engineering and computer-based technologies. In addition, many of the screening staff have affiliations with therapeutic areas, such as neuroscience or immunology. Screening developed into both a science and an art. As a result, the scientists involved in screening needed a forum through which to interact, exchange ideas and develop and evaluate new technologies. In mid-1994, the Society for Biomolecular Screening (SBS) was conceived, bringing the new science of screening under one umbrella.

Exchange of information

The SBS is designed to enhance the exchange of information concerning the science of screening, including topics such as assay design, sample diversity, information management, automation and access to screening resources. The SBS sponsors short courses, working groups and publications, and has a dedicated quarterly publication, the *Journal of Biomolecular Screening*. The SBS also has a Web homepage (http://sbsonline.com) and has created 'Society Forum', which gives members the opportunity to exchange ideas.

The Society is governed by a council of nine members. The council has both industrial and academic representation, and each member has expertise in screening and screening technologies. The council elects the officers of the SBS. The office of the society is in Danbury, CT, USA and the office staff are accessible via e-mail (C_Giordano@prodigy.com) and regular mail (36 Tamarack Avenue, Suite 348, Danbury, CT 06811, USA).

There are now approximately 600 members in the SBS, and it continues to grow. Members are drawn from the pharmaceutical and biotechnology industry and equipment and reagent manufacturers, as well as from the academic community. Many new technologies have an academic origin and an interaction with the industrial partners has allowed the timely application of such technologies. Funding for the society is primarily through membership, corporate contributions and conference fees.

Meetings and awards

The 1996 Annual Meeting of the SBS, held in Basel, Switzerland, was well attended and involved lively discussion. The 3rd Annual Meeting will be held in San Diego on 22–24 September 1997. The program for this meeting is ambitious and has been expanded to include new areas for screening such as genomics and microrobotics. The SBS has instituted its first award – The Walllac Award – for innovation in HTS.

As screening continues to expand its scientific base and influence in the drug industry, the SBS will gain strength and will play a central role in defining the future of screening.

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