Dr Stacia Sower outlines her laboratory’s ongoing research in identifying key reproductive hypothalamic and pituitary hormones in lamprey, which could provide the scientific basis for better medical therapies and an effective fisheries management strategy.

Can you summarise the focus and objectives of your research?

The major goal of my current research has been to test the global hypothesis that lamprey have a hypothalamic-pituitary-gonadal axis. The specific objectives of our GnRH receptor work are to characterise:

- Lamprey GnRHR-2 and 3 sequences and perform phylogenetic analysis to determine function in second messenger activation assays and ligand-binding specificity
- Key functional features of lamprey GnRH receptor-1, 2 or 3 (type-II receptors) by site-directed mutagenic studies
- Differential signalling properties and the mechanisms of the termination of the intracellular signalling attributable to the C-terminal tail of lamprey GnRH receptor-1, 2 or 3 by using transient cell lines that express either full-length or point mutants

What, specifically, do you anticipate will be the key outcomes of your research?

Identification and functional studies of novel GnRH receptors from basal vertebrates can provide valuable information on the complexity and molecular delineation of the interactions of GnRHs and their respective receptors, and provide considerable insight and clarification into the molecular basis for transmission of the signal to the G protein or other signalling pathways. Understanding the comparative aspects of the structural elements of GnRHs and their receptors can lead to the development of novel interventive GnRH analogs for better medical therapies or for use in controlling reproduction in fish aquaculture. A new method of sterilisation would also be very useful in the field of sea lamprey control in the Great Lakes.

In what ways have your laboratory and collaborators been a major force in demonstrating the value of the sea lamprey as a model system for evolutionary analyses? Indeed, can you expand on why the sea lamprey is considered a viable and useful model?

As an agnathan, the oldest extant lineage of vertebrates, the sea lamprey has become a model system for analysis of the evolution of many genes and systems including the evolution of the neuroendocrine regulation of reproduction and the evolution of development (EvoDev). Lampreys as basal vertebrates were identified to be integral to evolutionary studies; as such, the mapping of the lamprey genome started in Jan 2005 (www.genome.gov/12511858). Nine non-mammalian organisms were chosen by the NIH for mapping the genome, each of which represents a position on the evolutionary timeline marked by important changes in animal anatomy, physiology, development or behaviour. It is estimated that the current coverage of the genome is about 5.9X, which infers that much of the genome has been sequenced and available for analysis using the trace archives and the partially assembled genome by Ensembl.

Findings from your laboratory have illustrated that the acquisition of the hypothalamus was a seminal event in vertebrate evolution. To what extent – and in what sense – do these findings constitute a major breakthrough in research?

Our existing data suggest the existence of a primitive, overlapping yet functional hypothalamic-pituitary-gonadal (HPC)
and hypothalamic-pituitary-thyroid (HPT) endocrine systems in this organism, involving one or possibly two pituitary glycoprotein hormones and two glycoprotein hormone receptors as opposed to three glycoprotein hormones interacting specifically with three receptors in gnathostomes (vertebrates with mouths and jaws). We hypothesise that the glycoprotein hormone/glycoprotein hormone receptor systems emerged as a link between the neuro-hormonal and peripheral control levels during the early stages of gnathostome divergence. The significance of the results obtained by analysis of the HPG/T axes in sea lamprey may transcend the limited scope of the corresponding physiological compartments by providing important clues in respect to the interplay between genome-wide events (duplications), coding sequence (mutation), and expression control level evolutionary mechanisms in definition of the chemical control pathways in vertebrates.

Can you shed light on your collaborations with laboratories based at the universities of Kitasato and Niigata, Japan? How have these laboratories contributed to the project’s aims?

I, along with Professor Hiroshi Kawauchi of Kitasato University in Japan, have shared students and researchers through a formal collaboration that has produced more than 30 papers. Professor Kawauchi (now retired) and two associates, Drs Takahashi and Moriyama, have been collaborating since 1985. Some of the many ongoing projects in my laboratory are collaborative studies with my Japanese colleagues. It all began because we were trying to identify the lamprey Gonadotropin (GTH) in 1985-6. We thought it would take maybe two years. In fact, it took us a little over 20 years and we reported our results on the identification of lamprey GTH beta. Most recently, we have now published on the identity of hagfish GTH.
INTRODUCTION

INSIGHT FROM LAMPREY GENOME: STRUCTURE-FUNCTION STUDIES OF NOVEL GNRH RECEPTORS

OBJECTIVES

The laboratory’s ongoing studies focus on the molecular, biochemical and functional studies to test the overall hypothesis that lamprey GnRHs, GTH and their receptor(s) share common functional and developmental features compared to later evolved vertebrates. The research embraces new methodologies that are becoming available through the disciplines of hormonal genomics, proteomics and bioinformatics.

KEY COLLABORATORS

Professor Hiroshi Kawauchi, Kitsato University, Japan
Professor Masumi Nozaki, Niigata University, Japan

KEY FORMER GRADUATE STUDENTS

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STACIA A SOWER received her BS degree from the University of Utah in 1973 and her MS and PhD degrees from Oregon State University, USA, in 1978 and 1981, respectively. She is currently a Professor and Director of the Center for Molecular and Comparative Endocrinology at the University of New Hampshire, and is also a member of the North American Society for Comparative Endocrinology Council (2010-).

several neuroendocrine and environmental factors. Drawing on this, Sower comments: “In order to control fish puberty or sterilise fish, we need to understand the underlying mechanisms that trigger and control puberty”. She continues: “The ongoing research in my laboratory is to further identify key reproductive hypothalamic and pituitary hormones in lamprey and to determine interrelationships of these hormones under specific reproductive stages and environmental conditions”. Sower’s team of dedicated researchers anticipate their programme will provide key findings which will contribute to the development of better medical therapies and novel strategies for controlling reproduction in fish.

REARING ITS ANCIENT HEAD

In focusing upon lampreys – that is, the oldest extant species on Earth – Sower’s research bears enormous relevance in determining neuroendocrine development in evolutionary terms. Indeed, landmark findings that have recently emerged from Sower’s laboratory illustrate that the acquisition of the hypothalamus in lamprey was a paradigmatic development in vertebrate evolution. She observes: “The hypothalamic-pituitary (HP) system is considered to be a vertebrate innovation and seminal event that emerged prior to – or during – the differentiation of the ancestral agnathans [jawless fish]”. Despite the highly diverse life cycles and reproductive strategies and behavioural patterns of vertebrate fish species, the endocrine system observed by Sower and her team is, somewhat incredibly, conserved throughout gnathostome (species bearing mouths and jaws) lineages.

FINDINGS AND NEW HYPOTHESES

Sower’s team has adopted a multidisciplinary approach to investigate the structure and function of GnRHs in lamprey. By assimilating biochemical, molecular, immunocytochemical and functional studies, the team has determined that the lamprey possesses a hypothalamic-pituitary-gonadal axis and that there is a high conservation of the mechanisms of GnRH action. However, while Gnathostomes are generally seen to have two GnRHs that act as hypothalamic hormones, lampreys are the earliest evolved vertebrates for which there are demonstrated functional roles for three GnRHs that act via the hypothalamic-pituitary-gonadal axis controlling reproductive processes. Coupled with this, Sower’s group has identified GnRH receptors in lamprey which share several characteristics seen in type-I and type-II vertebrate GnRH receptors. Highlighting the significance of these findings, Sower states: “The high conservation of GnRH and its receptor throughout vertebrate species makes the lamprey model highly appropriate for examining the GnRH system in terms of its ligands and novel receptors”. Furthermore, the team has recently located a novel GnRH (called 1GnRH-II) and two novel GnRH receptors (lGnHR-2 and 3). This discovery has provided a unique opportunity for comparative and evolutionary analysis of the neuroendocrine system in vertebrates.

Within this evolutionary context, Sower and her collaborators have formulated a new hypothesis relating to the neuroendocrine control of reproduction in lamprey. The team proposes that the neuroendocrine and thyroid functions in the agnathan sea lamprey are simpler than those exhibited in later vertebrates. This is based upon the formulation that in lamprey, one glycoprotein putatively interacts with two receptors. “In our research, this transforming paradigm serves as a model for analysis of the evolutionary mechanisms leading to emergence of the highly specialised Gnathostome endocrine axes,” Sower affirms.

ROLE OF GENOMICS

As a marker of how much our understanding of the neuroendocrine system in lamprey has advanced, Sower recalls the paucity of knowledge that had been gleaned when she first entered the field: “When I started my studies 30 years ago, most scientists did not think that the lamprey had the same neuroendocrine system as all other jawed vertebrates. This was an animal with a backbone that we did not know anything about”. Today, however, studies in this area are enhanced enormously by the mapping of the lamprey genome. Indeed, the advent of genomics has proven critical in the identification of ligands, receptors, transcription factors and signalling pathways. Although the lamprey genome has not, as yet, been fully annotated, efforts are well underway, with Professor Weiming Li of Michigan State University leading a battery of international scientists in this pivotal endeavour.