University of Victoria: Department of Biochemistry and Microbiology

# The Second Messenger

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## Computer Software Provides a New Weapon in Disease Control

Work in the laboratory of Dr. Chris Upton achieved a particularly high profile during last year's SARS outbreak. Sequence information collected by Vancouver labs on the SARS virus was sent to his lab with a request for annotation. Using bioinformatics tools Upton and Dr. Rachel Roper were able to decide which proteins could be expressed by the virus, along with various other related data, over the course of a weekend. This ultimately proved a crucial step in publishing the first sequence for the SARS virus.

*Dr. Chris Upton in his office at UVic*

While Upton's particular specialty is viruses, very little traditional virologyis is currently being done in his lab. Though sequencing of a variety of poxviruses goes on in the hands of graduate students, the central focus is the emerging field of bioinformatics. The very nature of the subject has therefore generated an environment in which people trained in computer science are every bit as vital as biochemists and microbiologists.

Bioinformatics takes advantage of the tremendous advances made in data management through computers in order to aid in the analysis of genomic and proteomic information obtained in the lab. The basic idea behind the concept is simple. By loading all available data into huge, publicly accessible databases, it should be possible to run comparisons on newly obtained sequences. This may identify similar genes or proteins which can then be used to extrapolate the functions of those elements of interest to a researcher. Similarly, the often subtle differences between virulent and attenuated strains of a pathogen may be examined in detail.

Whether the information gathered is structural or purely functional, this process is of vital importance. Critical functions in pathogenesis can be rapidly identified as can antigenic targets on the surfaces of viral capsules. A researcher is then at a real starting point for the development of new drugs and vaccines far sooner than would be possible otherwise.

For all the promise of bioinformatics, there are problems at this stage in the development of its techniques, and this is where Upton's team steps in. The huge diversity in the bioinformatics programs available poses a problem. To maximize the usefulness to a researcher, it must be simple and fast to enter new sequences in the database. No less important, it must be an easy process to examine data, and compare it with other sequences. The interfaces and tools should maximize user friendliness so that the processes of bioinformatic analyses are not long and arduous ordeals.

To this end, Upton's lab is working on the development of several new software tools. Aside from the obvious need to generate a comprehensive database, beyond the myriad of specialized ones out there, new functions are also being worked on to make the life of the researcher easier. From annotating genomes and correcting existing annotations, to more efficient ways of comparing sequences, the efforts are exhaustive. The end result will be systems that do not require software experts to run analyses for the scientists who experimentally collected the data.

While Upton's work will be widely applicable, it is unique in its focus on support for viral research. Though Canada has been active in the development of bioinformatics, this area has been neglected. When one considers the comparative lack of effectiveness in treating viral disease as opposed to bacterial, the need for viral bioinformatics is clear. This has helped the project to warrant a five year grant from NSERC totalling $300,000.

In a world where it seems that new pathogens are appearing with greater frequency, a well organised approach to disease control is vital. Together with his team, Chris Upton's contribution to medical research may be to facilitate identification and characterization of emerging pathogens.

# Transgenic Peptide Expression Gives Hope for Broad Pest Resistance in Crops

Every year, billions of dollars in crop losses result from the damage done by infectious organisms. Killing crops in the field, or leading to premature spoilage, the result is a significant impediment to world wide food distribution. Through novel approaches in the development of transgenic plants, new crops are on the horizon which may be far more resistant to disease than anything that we've had before.

*Dr. Santosh Misra holding a transgenic potato plant*

Work is underway in the laboratory of Dr. Santosh Misra that addresses one of the fundamental problems pertaining to food supply. The focal point of her research has been cationic antimicrobial peptides. Discovered over the past couple of decades, these small macromolecules have a significant capacity to kill microorganisms. The positive charge of these peptides allows interference with the integrity of the microbial membrane. Perhaps more importantly, recent research has shown that the peptides interact with the host immune system. This interaction has a synergistic effect, allowing the host to fight off infection far more readily than it would be able to otherwise.

With early funding from an NSERC Strategic grant, and later by the National Centre of Excellence for Microbial Disease, Misra set to work on the problem of just how these peptides might be used to protect plants. The answer has been to use established genetic engineering methods (such as the use of *Agrobacterium tumefaciens*) to transform plants with the genes that will allow them to produce cationic peptides. With an enormous diversity in the peptides to be found in nature, transformation may well have been the simple part.

Many of the cationic peptides found in various sources in nature are unsuitable for one reason or another. Certain strains found in barley, for example, had inadequate antimicrobial activity. Others, such as melittin, which is the major component of bee venom, produce side effects that make them unsuitable for application. The solution has been the creation of chimeric peptides that use components of more than one existing system to achieve the desired results.

Tested so far in the development of disease resistant potato and tobacco plants, the work has been a rousing success. Subjected to challenge by organisms such as *Phytophthora cactorum* (causative agent of potato late blight), transgenic plants remained healthy while control plants withered and died. Whether challenged by fungal or bacterial pathogens, the versatility of the positive results was astounding. Given the vulnerability of potatoes to destructive fungal diseases such as potato late blight, the usefulness of this process is clear.

Beyond the purely protective nature of the peptides, a wider range of concerns has been diligently addressed. Among the first of these has been the effect on the plants expressing the molecules. Looking deeper than the overall health of the plants developed, it has become clear that the production of these proteins does not inhibit growth or other functions. Effectiveness of the peptides is somewhat species specific though, requiring that different peptides be developed for different plant systems.

The obvious question of just how healthy these plants are for ingestion has also been examined very carefully. In mice it has been shown quite definitively through testing that the cationic peptide containing transgenic potatoes have no adverse effects on the animals. This conclusion was drawn by comparison to a control group fed equal amounts of non-transgenic potato.

The work over the years has produced a number of patents from Misra's lab. Of these, the most important at the moment is probably Protectin® technology which has been licensed to SynGene Biotek. Founded in 1996 by Misra, Syngene is a spin-off of the UVic Innovation Development Corporation. Since its inception, the company has received funding from the National Research Council Industrial Research Assistance Program in order to further develop and refine its technologies. In the pipeline, is work to expand broad range protection to important crops such as wheat and canola.

Despite some public controversy over genetic engineering in general, there seems little doubt that Dr. Misra's work will prove to be of paramount importance. In a world with an ever expanding population, the benefits of a larger viable crop base are clear. Further, replacing the use of existing pesticides and antimicrobial agents, to which resistance readily develops, has its own advantages. Longer term protection comes hand in hand with healthier food that is free of the toxins that would have been sprayed on them otherwise.

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# Learning Bioinformatics for the Information Age

New this year in the Biochemistry and Microbiology Undergraduate program has been the implementation of Bioinformatics labs. Intended to familiarize students with the techniques involved in the field, the skills imparted are invaluable. Even in its infancy, biotech companies are rapidly recognizing the need for people with experience in the electronic manipulation of data.

The task of putting together an effective laboratory package fell to instructor Judy Wise with the help of Melissa de Silva. Approaching the problems faced like a student would have to, she read and reread a lot of available literature on the subject. Searching the internet, she learned more about the available assortment of tools and their uses. All of this considered, she endeavoured to assemble a balanced package that would give the undergraduates an effective introduction to bioinformatics.

The results of Wise's efforts were a success, far beyond what she had hoped. Students enjoyed the lab and were able to approach the material with remarkable proficiency. Much of this was due to a level of computer literacy that was better than expected, but this only helped them focus on the important details of the exercise. Whether they were searching for matching DNA fragments, or locating the structure of a determined protein, the flexibility and value of the tools was made clear.

For this year, only one bioinformatics lab was prepared for use by the third and forth year students together. Given that the lab was somewhat experimental, and that none of the students had any experience up to this point, this seemed the best approach for the moment. As the third year's roll into fourth in the coming fall, they will face a new, more challenging assignment and with it be able to sharpen their skills still further.

*Microbiology 301 students working on Bioinformatics*

# Changes to the Biochemistry/Microbiology Undergraduate Program

As with all programs at UVic, the Biochemistry and Microbiology undergraduate programs are constantly evolving. September 2005 will see changes in the first and second year for both disciplines, with additional changes to the Microbiology program in third and fourth year. The intent of these changes is to give students in both disciplines a broad basis in the life and physical sciences in the first two years, while allowing them to specialize more in one of the disciplines during their last two years.

Students in our programs have always had a solid grounding in chemistry. However, in recent years there has been no requirement for biology courses. In order to put the BIO back in BIOchemistry and MicroBIOlogy, the first year now requires introductory Biology. Although one of two English courses had to be dropped to make room, the Department remains the only one in the Faculty of Science with an explicit English requirement. Other changes allow students greater flexibility in their choice of Math and Physics courses in first year. The biology background of students is expanded in second year with the inclusion of a cell biology course. A course in statistics, an increasingly important tool for those in the life sciences, replaces a second course in calculus.

Third and fourth year in Microbiology have been changed in order to allow students to take more biology courses. Physical and inorganic chemistry have been replaced with cell biology and molecular genetics in third year. Biochemistry students continue to take these advanced chemistry courses. Fourth year Microbiology students now have the option of choosing three courses from amongst virology, immunology, molecular biotechnology and ecology of prokaryotes, instead of two. The full year biochemistry course in third year has been split into two one-term courses, to better accommodate co-op students in both disciplines.

# Congratulations

To Paul Romaniuk and Chris Upton for the renewal of their NSERC grants, and to Lindsay Frehlick (Juan Ausio's lab) and Eric Tran (Brad Nelson's lab), recipients of NSERC postgraduate scholarships.

# Approaching the Law from a Scientific Background

Working in the lab of Dr. Chris Upton, aided by, but apart from the prominent bioinformatics, is Christine Butler Cole. One of the graduate students in the Department, she is working in Upton's lab as she completes her degree. While many of the students coming up through the various levels of the Biochemistry and Microbiology program have ambitions of entering the scientific workforce, or going on and doing a doctorate, she has come to a different decision. Adding to the knowledge gained through her studies in the Department, she plans to add the sudy of law to her repertoire.

The work that Christine has been involved in has been both interesting and important. Researching poxvirus, she has cloned genes that encode viral proteins. This study is of particular importance because many of the protein products are unknown. The process is complicated by the fact that not all of the genes in question are easily cloned and expressed. In the end, the value of such efforts is clear however. Carrying out assays such as immunoprecipitations along with a bevy of other tests, an understanding of the function and mechanisms of these proteins begins to take shape. This information holds promise for the development of new medical treatments in the future.

Despite her enjoyment of science, Christine found herself being drawn to a more diverse path. The decision to study law came about during the last couple of years as she got a better feeling for what was going on in her own lab, and the Biotech industry in general. She began to see that law can change the directions in which research, and the resultant discoveries travel. Whether it be as a result of government regulation, or patent issues, the influence of law can not be denied. As a result, many discoveries which are scientifically sound, may never make it to product stage.

*Christine Butler Cole in the lab*

Doing a doctorate in biochemistry is an option that Christine seriously considered before deciding on law. This would have allowed her to participate in a lot of important research and certainly had its appeal. Finally though, she came to the conclusion that this wasn't for her. Instead, making use of her background in science, she has decided that the best way in which she can make her own mark is to work through the law, helping to move the fields of biochemistry and microbiology forward.

With her goals firmly set, Christine has already applied to the law departments at UVic, UBC and the University of Calgary. Driven, and passionate about making certain that important discoveries don't slip through the cracks, there seems little doubt that she will excel in her pursuit of a law degree. Working within the lab, or outside, Christine sets a fine example of the multitude of careers open to science graduates..

# Undergraduate Earns NSERC Award

While perhaps not so recognized as the more senior students within any faculty, it is the undergraduate students who form the real base from which the scientific elite of tomorrow will be born. Within this group there are many levels of skill and accomplishment, with a few people standing out early on. One such person is Anna Burianova, a student currently well into her third year of a Bachelors Degree in the Department of Biochemistry and Microbiology at UVic.

As a particular point of achievement, Anna was given an award for Women in Science and Engineering through NSERC. Awarded to only twenty-five young women in Canada each year, this provided the opportunity to work for three years, gaining invaluable experience in the fields of biochemistry and microbiology.

Winning the award required that Anna meet several criteria that could tax anyone's abilities. Application for the award required that she be able to supply a pair of strong reference letters from the faculty, as well as an essay detailing why she felt the award provided such an excellent opportunity. Further though, she needed an excellent grade point average, and just as importantly, practical research experience, which she had working with Microtek, a UVic company.

The award brought her to a number job offers through NSERC. However, she has demurred in favour of a position that she hopes to get with the BC Cancer Agency. Fitting better with her plans to finish her undergraduate degree next year, this will put her more directly on the road to her medical doctorate. In the meantime, Anna continues with her course work while attending to directed studies under Dr. Levin. Unfortunately, the award program itself has been cancelled due to budgetary reasons, but moving up through the Department program quickly, she provides a shining example for countless students who hope to someday achieve similar levels of excellence.