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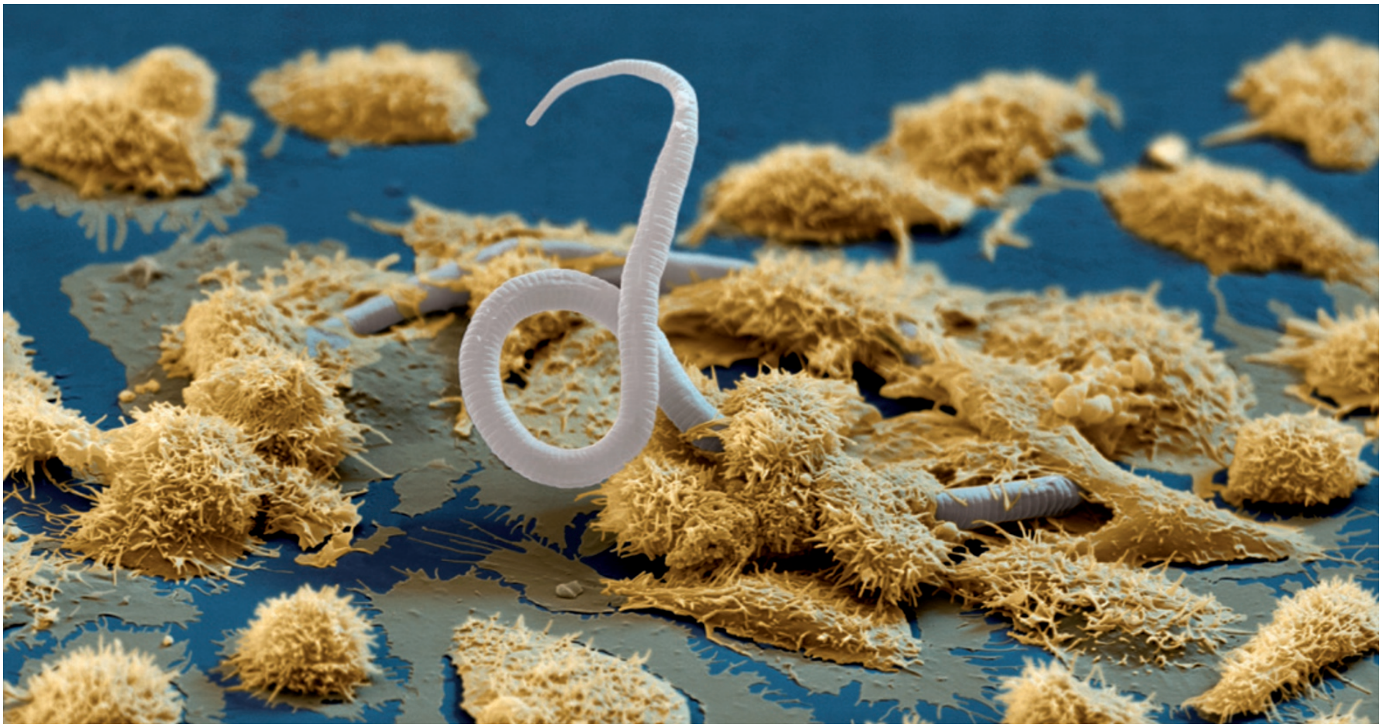

Systems immunologists track the effects of drugs and infectious agents, such as parasitic worms, on the body's defences.

SYSTEMS IMMUNOLOGY

Complexity captured

Researchers who can grasp the intricacies of the immune system and enjoy distilling meaning from large data sets are in demand for a growing subfield of systems biology.

BY CHARLOTTE SCHUBERT

Lisa Israelsson grips her head in her hands, pink hair peeking through her fingers. She has hit the wrong key on her computer, and now she can't find the 1,511,104 data points that she had been working on. But that's the least of her worries — once she has retrieved the information, she will have to work out what it all means.

The numbers are ranged on a spreadsheet with 47,222 rows and 32 columns. Each column corresponds to a blood sample taken from a person with an immune-system defect. Every sample has been processed and placed onto a microarray chip dotted with 47,222 unique DNA molecules to measure which genes in the sample are active, which are inactive and which are expressed at unusual levels. It is going to take Israelsson, an immunology postdoc with little experience in computational biology, about a week to crunch the information and turn it into tidy charts that will provide quick snapshots of the state of each person's immune system.

Fortunately, Israelsson can turn for help to any of the researchers in her lab, who include molecular biologists, biostatisticians, bioinformaticians and a software engineer who once designed an electronic billing system for the government of Bhutan. The lab, at the Benaroya Research Institute in Seattle, Washington, is run by Damien Chaussabel, a systems immunologist. Using readouts of the immune system such as the one that Israelsson is preparing, the lab aims to develop molecular signatures for immune-related conditions from sepsis to lupus, to better diagnose patients and predict how they will respond to drugs and vaccines.

Chaussabel's cooperative, interdisciplinary team is typical in the burgeoning field of systems immunology, a loosely defined subspeciality of systems biology. As the name implies, systems biology measures how molecular components such as genes, proteins and cells interact within a system — from a biological tissue to an entire organism — and uses computational mathematical methods to describe the system and predict how it will behave if its components are perturbed.

Until a few years ago, systems biology was dominated by the study of yeast cells and tumours, which have a manageable number of components. The immune system, with its ▶

dozens of different cell types and hundreds of intersecting molecular pathways and signals, has proved more difficult to model. But now, researchers are taking up the challenge.

A systems approach can help immunologists to predict, for example, how the immune system will respond to a particular vaccine or drug — will it react in a way that will ease disease? Or will a drug that is under development cause undesirable side effects?

Encouraged by early successes of systems-biology approaches in cancer research — including the commercialization of diagnostic gene chips — and by technological advances in the large-scale analyses of molecules, systems immunology is in a growth stage: funding is expanding, creating job opportunities for researchers at all stages of their careers. Although much of the demand in academia is coming from the United States, there are also opportunities in Europe and Asia. And pharmaceutical companies worldwide are hiring systems immunologists at all levels to help pick out potential drug targets on the basis of models of immune-system function, or to monitor the immune systems of subjects in clinical trials.

GROWING SUPPORT

In Seattle, not far from where Israelsson is working on her data set, Alan Aderem's 45-member systems-immunology lab is in the middle of moving from the Institute of Systems Biology, which Aderem co-founded, to the Seattle Biomedical Research Institute (SBRI), which he will now head. The move shows how interest in the field of systems immunology is growing. It was financed by a US$7-million grant from the Bill & Melinda Gates Foundation in Seattle, which, among other work, supports research into infectious diseases that affect the developing world. Aderem's lab will bring a systems approach to the SBRI's current focus on infectious diseases, including HIV, malaria, tuberculosis and leishmaniasis.

Funding agencies in the United States are helping to propel the field's expansion. Chaussabel's research is funded largely by a five-year, $100-million US National Institutes of Health (NIH) grant to the Baylor Institute for Immunology Research in Dallas, Texas — where Chaussabel was based until last year and still holds a part-time appointment — and six other centres nationwide that are part of the NIH's Human Immunology Project Consortium. The consortium aims to generate molecular signatures of the human immune system and its response to vaccination and infection.

The NIH also spends millions of dollars on systems immunology outside the consortium. For example, the largest formal systems-biology programme on the NIH campus is in systems immunology, says Ron Germain, an immunologist at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, who launched the scheme in 2008. His programme had a budget of $4.1 million last year, is hiring a fifth principal investigator, and will employ dozens of postdocs, technicians and other staff as it develops.

But Chaussabel cautions that as with any new discipline, systems immunology will continue to grow only if it proves successful; for example, if researchers can come up with improved approaches to HIV-vaccine development or new diagnostic tests for a variety of diseases. "You need to see some deliverables in the short- to mid-term before the field gets very large," he says. However, Chaussabel, Aderem and others in the field are optimistic about prospects for systems immunologists in academia and industry. "In an environment where all jobs are really tight," says Aderem, "systems biologists, the good ones, have their pick to a large extent."

GLOBAL PROSPECTS

Major funding agencies outside the United States have not embraced systems immunology with as much enthusiasm as the NIH. But projects are starting to emerge worldwide.

Last year, for instance, John Connolly of the Singapore Immunology Network started a systems-biology lab that focused on the human immune system. His group has big ambitions: he aims to collaborate with drug companies and researchers throughout Asia to monitor the immune responses of subjects in clinical trials and identify molecular signatures that predict outcomes or side effects.

"Every day there is something new."
Lisa Israelsson

The European Union (EU) has not funded any efforts comparable to the Human Immunology Project Consortium, says Stefan Kaufmann, director of immunology at the Max Planck Institute for Infection Biology in Berlin. But EU researchers can obtain grants for smaller systems-immunology projects. In Kaufmann's lab, for example, a study of tuberculosis is funded in part by SysteMTb, a four-year, €10.5-million (US$15.2-million) project launched last year and financed by the EU's research-funding framework, which brings together systems biologists and tuberculosis experts at 13 institutions across Europe.

Academia is not the only area in which opportunities are growing. The pharmaceutical industry worldwide is hiring systems immunologists, from newly minted PhDs in biostatistics, bioinformatics, pharmacodyamics and other computational fields to immunologists and molecular biologists who have spent years as postdocs or academic faculty members.

The increased demand in recent years has coincided with the overall contraction of pharmaceutical research budgets, so it is difficult to ascertain whether there is an overall uptick in industry job openings, warns Debraj GuhaThakurta, who heads the systems-immunology group at Dendreon, a biotechnology company based in Seattle.

The greatest demand for systems immunologists in industry is at large pharmaceutical companies that are developing vaccines or other agents that affect the immune system, such as monoclonal antibodies, says Aderem. Those companies include Novartis, based in Basel, Switzerland, and Sanofi–aventis, headquartered in Paris.

WHAT IT TAKES TO GET THE JOB

Those interested in a career in systems immunology should get experience in both systems biology and immunology, says Aderem. He advises immunology graduate students to spend some time in systems-biology labs, and quantitative experts, such as biostatisticians and bioinformaticians, to learn some immunology. GuhaThakurta, who has a PhD in biophysics, boned up on immunology through reading and coursework for six months before applying to Dendreon. Institutions such as the University of California, Irvine, are also starting to offer graduate programmes that combine specific fields of biology with training in systems biology.

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In comparison with other fields, systems-biology labs hire a lot of staff scientists, who have greater job security and higher salaries than postdocs. Aderem's lab, for instance, employs 13 research scientists, a set-up that aims to foster long-term collaboration.

Applicants will find that the abilities to work in a team and think outside their areas of training are important in this multidisciplinary area of research. Such qualities are particularly valued in industry, where systems immunologists interact on a daily basis with chemists, pharmacologists and clinical-trial designers. Industry also seems to place a premium on scientists with experience in translational research, says GuhaThakurta.

Many biologists are intimidated by the computational side of science, and computer scientists can be perplexed by biological questions, but to be successful in this field "both groups need to be prepared to get out of their comfort zones", says Aderem.

It is just that adventurous quality that led Israelsson to Chaussabel's lab and allowed her to tackle systems immunology. Israelsson and a colleague, a computational biologist, are now coaxing her data out of hiding. When they have finished, Israelsson will learn how to use software that tells her which genes in the people in her study are going rogue. Her work, says Israelsson, is never boring. "Every day," she says, "there is something new." ■

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