

Researchers focus on inflammation at the Istituto Clinico Humanitas

With international recognition as a premier medical institute, the Istituto Clinico Humanitas pulls disease questions from their patients in the clinic into their preclinical work in the lab. **Kristin H. Kain** investigates.

The body responds to most diseases with inflammation. The inflammatory response may be beneficial, exposing and killing unwanted invaders, or deleterious, triggering and aggravating disease. In both cases, inflammation provides a common thread that is deeply involved in most pathologies.

'Inflammation underlies a diversity of human pathology from cardiovascular disease, central nervous system degenerative disorders, cancer and, of course, immunological disorders,' says Dr Alberto Mantovani, the Scientific Director of the Istituto Clinico Humanitas. The scientific approach at this Italian research center is guided by their belief that identifying and untying the threads between inflammation and disease will unravel a variety of human disorders and improve overall patient care.

The Istituto Clinico Humanitas in Milan, Italy, was born from an established clinic with over 700 beds devoted to both inpatient and outpatient care. The clinical division of Humanitas originated in 1996 with a €160 million investment to support medical technology and innovation. In addition to its inpatient care facilities, 115 outpatient clinics are contained in its 60,000 square meters.

Dramatic growth in the last 3 years has brought almost 120 primary preclinical researchers into its folds, despite little increase in investment by the Italian government over recent years. Scientists apply for external funding to support their research projects. To facilitate this, the institute maintains affiliations with many local and international charities that provide medical funding, including the Italian Association for Cancer Research, Cariplo Foundation and the Telethon Foundation.

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Fig. 1. Istituto Clinico Humanitas Research Center.

The focus on immunology and inflammation at Humanitas grounds the institute in a common set of goals and understanding. Finding people with expertise in relevant areas directs their recruitment strategies. 'Our philosophy is not to be spread out in our research efforts, but to have a critical mass, because we want to have an impact,' says Mantovani. He finds that the common language and mission throughout the institute inspire a sense of community that naturally draws clinical experience into their research. 'It allows us to talk with each other and to interact with various segments of our clinic.' It is easy for researchers to become lost or confused in the vast milieu of medicine and they find that students, postdocs and faculty are attracted to the centralized approach at the institute.

Their immunology focus also encouraged an extension of their interests into the pharmaceutical sector. They recently joined efforts with Intercept Pharmaceuticals to develop therapeutics for gastrointestinal inflammatory disease. 'We are interested in them because they have a focus that is absolutely coincident and complimentary to ours,' says Mantovani.

The partnership between US-based Intercept and the Istituto Clinico Humanitas is one example of the global ties woven in and out of their research. Participation in international research and listening to comments from creative minds with varied backgrounds is a priority. External collaboration facilitates the work at the institute and is meant to keep their research timely and informed. 'For instance,



Fig. 2. Dr Alberto Mantovani, Scientific Director of the Istituto Clinico Humanitas.

in the area of oncology, there is a program that we have with the University of Miami. We compare methods of total cancer care, intervention and patient profiling,' indicates Mantovani.

The institute also seeks feedback from its international partners. For example, the Istituto Clinico Humanitas is the first Italian clinical institution to be accredited by the Joint Commission, an independent US non-profit organization that designs clinical care benchmarks and performs evaluations of healthcare programs and institutes. These types of interactions are intended to provide a rich source of ideas from the larger scientific community.

'We are obsessed with the concept of being evaluated as an institution and in having our people evaluated. This is key to us,' says Mantovani. The clinicians and scientists at Istituto Clinico Humanitas receive input from an international advisory board with expertise that reflects their focus on immunology and inflammation. The advisory board provides advice on platform and preclinical research, which includes basic science. This board boasts of a Nobel laureate and includes members from the USA, Switzerland and Italy. Ad hoc reviewers are flexible additions to the board's membership to include the necessary areas of expertise as research programs develop and change their scope.

An outside evaluator on a trip to the institute can expect to first meet with stu-

dents and training-level scientists and discuss their work through poster sessions. They then discuss the work of individual primary investigators with Dr Mantovani, who in turn is the subject of review when the ad hoc reviewer meets with the CEO (chief executive officer) of the clinic and the president of the institution. Mantovani does not mind his personal evaluations since he feels that 'getting critical feedback helps to keep us on track during this period of dramatic growth.'

There is a careful strategy to the growth at the institute. Researchers are encouraged to use their experience with patients to identify the issues that represent the most urgent patient needs. Most of the primary investigators are clinically trained and spend at least 40% of their time devoted to patient care. They are also relatively young. In Italy, the average age of research scientists (the *ricercatori*) is about 50. In an attempt to rejuvenate scientific discovery, the institute actively seeks clinician-scientists early in their careers, usually in their 30s.

So far, the existing faculty has personally recruited senior-level positions but, in the future, hiring will include applications submitted through open calls. 'A critical strategic choice was to recruit at least a minimum number of physician-scientists,' says Mantovani. 'We need that type of person as a catalyst for translation from the clinic.' They invite members on board that they

feel will steer the institute toward its goals to be modern, efficient and innovative.

Out of the five principles that define the mission of the institute, three are centered explicitly on bringing modern technology and innovation to their patient care and teaching practices. 'We have a wonderful group of pathologists who help us analyze both human and mouse samples,' says Dr Anna Villa, a clinically trained scientist who now spends her time on osteopetrosis research. Through the clinic and collaboration, scientists at the institute have access to important patient samples. The tight connection between research and patient care draws the patient experience into the laboratory.

Another way that the Istituto Clinico Humanitas infuses its science with innovation and youthful vigor is through research development programs. Within the institute, there are training programs for the equivalent of a Masters degree in biotechnology or a PhD. The institute also has a formal relationship with the University of Milan to provide external clinical and research opportunities to their students.

'Our institution hosts teaching programs from the University of Milan, including a separate track in the medical school which



Fig. 3. Dr Graziella Solinas performs research to understand the role of inflammation in colon cancer.

is science problem-based. This structure brings together aspects of teaching, patient care and research, Mantovani points out. The university campus dates back to the 15th century and now fosters modern basic and applied science programs for a proportion of its 65,000 students. The large student body should compliment the growth of the institute, providing them with young talent, whereas the institute offers students an innovative learning environment.

Research at the institute follows the seeds of discovery all the way to clinical application, a process that relies heavily on model organisms. 'Our approach is to look for the function of molecules relevant to patients through gene inactivation in animals,' explains Dr Cecilia Garlanda, a veterinarian and scientist at Humanitas. 'We develop animal models of pathology and determine the biological function of these molecules using gene-modified animals. The last step is to look for the involvement of the identified molecule in humans in the same patho-

logical process that we studied in the animal.' By translating information between humans and mice they are able to decipher the role of some important molecules in clinically relevant disease.

One case in point is the highly conserved soluble pattern recognition receptor pentraxin 3 (PTX3). Scientists at Istituto Clinico Humanitas first recognized PTX3 as a molecule that was upregulated during localized infections in otherwise normal patients. They isolated PTX3 from patients and identified its corresponding gene in mice. Knocking out the gene in mice provided a valuable tool, and further studies were performed using mouse models in conjunction with human cell culture systems.

They discovered that PTX3 helps patients fight bacterial and fungal infections and developed an ELISA assay with their pharmaceutical partners to recognize the human protein. This assay is now used as a diagnostic and prognostic indicator of inflammation in a range of pathologies, from heart disease and lung injury to intestinal is-

chemia. The researchers are hopeful that future work will describe a potential application for PTX3 in patient therapy.

The Istituto Clinico Humanitas carefully watches their publication numbers and are happy to see their impact factors growing. They hope that this statistic accurately predicts the future potential for the strategies that founded, and continue to drive, the organization. They strive to bring patient clinical needs into the lab by tapping the unique perspective of the physician-scientist. Their concentrated focus on inflammation creates a tight community that invites global input and ideas. The Istituto Clinico Humanitas is an IRCCS (a Scientific Institute of Admission and Care), indicating its recognition by the Italian Ministry of Health, and is also named as a center of excellence by Lombardy's Regional Government. Their accreditations and awards demonstrate the quality of health-care services at the institute and its ability to bring clinical relevance and utility to medical research.

Institutes around the world are employing a variety of approaches to bring clinical relevance to their scientific research and to encourage innovation. At DMM we want to learn more about the types and effectiveness of these strategies so we might present them to our readers. Please let us know if there is an institute that you feel we should feature in a future article by emailing us at dmmreviews@biologists.com.