Can you describe your background and what motivated you to study neurology and, more specifically, biomarkers in stroke patients?

Since beginning medical school, I have been intrigued by the interplay between the nervous and endocrine systems. Studying hormones in the peripheral blood in order to predict risk and prognosis in life-threatening neurological diseases, such as stroke, was a fascinating interdisciplinary approach.

During my residency at the University Hospital of Basel, Switzerland, I had the opportunity to work, not only with leading members of my own discipline, but also with outstanding endocrinologists – Professors Mirjam Christ-Crain and Beat Mueller. We conducted patient-centred clinical outcome studies focused on neuroendocrine biomarkers for outcome prediction in stroke patients. To gain further clinical research skills, I completed a stroke research fellowship (under the supervision of Professor Mitchell SV Elkind) and a Master’s in Biostatistics at Columbia University, USA, where I had the unique opportunity to expand on my previous studies by measuring the neuroendocrine markers I worked with in Switzerland in a large and diverse patient group. Subsequently, in Switzerland, I have begun to build my own research group at the University Hospital of Zurich.

Why are these markers important in the context of ischaemic stroke?

Each year, over 5 million people worldwide die from stroke, and at least one in six patients who survive will suffer another within five years. We are therefore eager to improve timing and quality of diagnosis, prognosis and optimal risk stratification, as well as secondary prevention. In this context, blood biomarkers may improve patient care, as they have already done in other fields.

How did you select a candidate biomarker for your research? What are the advantages of their use?

In our search for new blood biomarkers, we tried to find a marker that is produced in the brain, yet easily accessible in the systemic circulation. The marker should incorporate as much information about the body’s condition as possible. In other words, it should reflect the damage that has already been produced by the ischaemia, the damage that might still arise, as well as the body’s capacity to restore the damage.

Neuroendocrine markers have the potential to reflect the individual ‘stress-burden’, they allow access to an ancient ‘alarm system’ that directly and quickly provides information about disruption to homeostasis. To directly assess this system – also called the hypothalamo-pituitary-adrenal (HPA) axis – at the level of the central nervous system, corticotropin releasing hormone (CRH) or vasopressin can indicate HPA-axis activation. However, their measurement is challenging.
Stroke signatures

Researchers from the University Hospital Zurich are identifying stroke biomarkers to more effectively target secondary prevention, improve patient outcome and efficiency of healthcare systems.

**DURING A STROKE**, a blood vessel supplying the brain occludes. This immediately interrupts the supply of oxygen and nutrients, irreversibly damaging brain tissue. Stroke significantly impacts individuals and their families, and places a heavy economic burden on healthcare systems. Despite this, current tools to identify the cause and prognosticate stoke are limited.

Thus, there is a clear need for improved prognostic information for the benefit of both patients and clinicians. Blood biomarkers represent a potential tool for meeting this need, improving prognostic accuracy for risk stratification and decision making, and thereby patient outcome. Dr Mira Katan is working to make this a reality at the Neurology Clinic of the University Hospital Zurich, Switzerland. Katan, despite her young age, has established her own group to make stroke blood biomarkers a reality.

**NEUROENDOCRINE MARKERS**

Stroke-related biomarkers are likely to have the greatest impact in areas where information is most limited, such as risk stratification, prediction of complications and the determination of stroke aetiology. To address this need, Katan’s research has focused on such themes using a pioneering and holistic approach and, with her team, she has identified the most promising candidates.

Activation of the hypothalamo-pituitary-adrenal (HPA) axis or ‘stress axis’ is one of the first measurable responses to cerebral ischaemia. Neuroendocrine markers maintain homeostasis following tissue damage, with each ‘stressor’ influencing the final stress marker level. They are thus ideal prognostic biomarkers; integrating information from different systems and reflecting the global threat to the body. In addition, the candidates selected and evaluated by Katan are easily accessible and can be accurately measured.

**A NEW SIGN OF STRESS**

In 2006, Katan and her colleagues began to assess the potential of different blood biomarkers to improve risk stratification. Under conditions of stress, vasopressin is released alongside corticotropin releasing hormone (CRH), which stimulates the HPA axis. Measuring CRH and vasopressin levels would be a potential method for assessing individual levels of stress and, consequently, prognosis; but it is unfeasible because of their pulsatile secretion and short half-lives. However, a molecule released from vasopressin’s precursor, copeptin, represents a promising alternative; it is found in equal proportions to vasopression, also bypasses the blood-brain barrier and is much more stable. The team compared copeptin to the classical peripheral stress hormone, cortisol, and their results demonstrated an enhanced increase following substantial physical stress. In addition, copeptin’s levels were also capable of reflecting moderate stress.

With copeptin’s potential established, the next step for Katan was to understand its value as a marker of prognosis for acute ischaemic stroke. In a large derivation, and subsequent independent validation cohort study, her team measured levels of the peptide in stroke patients when they were admitted to hospital and assessed neurological outcome after three months and one year. Correlating the two, copeptin was shown to be highly predictive; even adjusting for risk factors, copeptin improved the current gold standard – the National Institutes of Health (NIH) Stroke Scale.

**IDENTIFYING THOSE AT RISK**

To compare the use of copeptin to other potential prognostic hormones, Katan’s team evaluated the prognostic value of a number of alternatives: “We investigated other hormones linked to the HPA axis, including thyroid stimulating hormone and growth hormone, in the same cohort,” outlines Katan. “All were, to some degree, associated with functional outcome and mortality, but copeptin was the only biomarker that added relevant prognostic information beyond that of established prognostic factors.”

Copeptin however, which is released in an equimolar ratio to vasopressin, can be measured easily. Thus, we selected copeptin as the candidate marker.

**Why is it important to address the risks associated with stroke-associated infections?**

Unfortunately, even in specialised stroke units, stroke-associated infection remains one of the major complications, with frequencies up to 65 per cent. Pneumonia and urinary tract infections are the most common complications and approximately one-third of patients with ischaemic stroke die during hospitalisation due to one or more complications. By identifying those patients who are vulnerable to infections early, we could prevent much suffering and many deaths.

**In what ways have collaborations assisted your research?**

Without a good team and inspiring relationships, meaningful research is not possible, so I am truly grateful for the opportunities I have had to meet, learn from and work with wonderful researchers all over the globe.

In order to improve clinical practice, well designed, large-scale, multicentre studies are necessary, and multilevel collaborations are a prerequisite to this. My work requires vivid crosstalk between diverse disciplines.
Beyond its ability to prognosticate overall 90-day functional outcome, Katan also found that copeptin identifies those at risk of problematic hospital complications and suggests patients with elevated risk of mortality.

Over 15 per cent of stroke patients will suffer another stroke within five years; having the ability to direct prevention methods at the underlying mechanism is imperative.

Not only does copeptin have diverse uses, it could also be applied to a wide range of patients and stroke subtypes: “Copeptin was found to be similarly predictive in the young and elderly; men and women; those severely and mildly affected; as well as up to 72 hours after symptom onset. It can be used for risk stratification in the whole stroke population,” Katan enthuses. Copeptin clearly shows great promise, but clinical implementation will not be immediate. Large randomised controlled trials are needed to prove that risk-stratification algorithms incorporating copeptin perform better than the existing processes, and the cost-effectiveness of such a method also needs to be investigated.

AETIOLOGIC CLASSIFICATION

Following her studies of risk stratification, Katan moved on to investigate the different causes of stroke. Aetiological classification is important because prognosis, risk of recurrence and management options differ greatly between subtypes. Considering that today over 15 per cent of stroke patients will suffer another stroke within five years, having the ability to direct prevention methods at the underlying mechanism is imperative.

A number of classification schemes have been developed, of which the Trial of org 10172 in acute stroke treatment (TOAST) criteria are the most commonly used for the five ischaemic stroke subtypes. However, even using a thorough TOAST evaluation, the aetiology of ischaemic stroke remains undetermined in up to 39 per cent of cases. These patients are missing potentially life-changing interventions.

BIOSIGNAL

To address this deficit, Katan is leading the Biomarker SIGNature of Stroke Aetiology Study (BIOSIGNAL). This prospective, multicentre project aims to identify aetiological blood biomarkers in ischaemic stroke patients and has begun enrolling patients across Europe and the US. The study also aims to identify the value of these biomarkers in predicting the risk of recurrence in patients. The three-year cumulative risk of a recurrent stroke, dependent on aetiology, is up to 25 per cent. At present, preventing recurrence relies on a broad approach to reduce risk factors associated with atherosclerosis, heart disease and metabolic disorders. However, more specific interventions, such as anticoagulation and surgery or stenting, need aetiological information. BIOSIGNAL aims to determine where the most promising biomarkers can help identify stroke aetiology and also predict recurrent stroke. In addition, the insights gained into the processes underlying different stroke subtypes may lead to more targeted diagnostic tools.

PATIENT-CENTRED CARE

Through the clinical implementation of rapidly measurable blood biomarkers to diagnose aetiology on admission, BIOSIGNAL could help identify patients who need specific preventive treatment, such as anticoagulants. This would dramatically improve secondary prevention, enhance patient outcome and reduce healthcare costs.

The outcomes of this work could have important ramifications for both patients and healthcare structures: “The use of rapidly measurable serum biomarkers for aetiological diagnostic assessment may enhance classification and thus improve the implementation of optimal secondary prevention, patient outcome and cost-benefit ratio,” Katan concludes.