Serendipity and thinking outside the box in cardiovascular research

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The term "serendipity" means occurrence of an unplanned, fortunate discovery, hence it is often used to describe interesting findings made by chance rather than planning. Etymologically, the word "serendipity" originates in the Persian fairy tale "*The Three Princes of Serendip*", in which the protagonists repeatedly make discoveries by accident and keen judgement. The word is reference to the land "Serendip", an ancient name for Sri Lanka. In modern times, serendipity has led to remarkable inventions, such as the Post-It® note, the microwave oven or the popsicle (1).

Over the centuries, serendipity has also played an outstanding role in the history of drug discovery. A classic example known to every medical student, is the discovery of penicillin in 1928 by Scottish scientist Alexander Fleming, who noticed antibacterial properties of a blue-green mold which had formed in a petri dish containing *staphylococci* that had been left open accidentally. Upon closer examination of the petri dish, Fleming discovered a halo of inhibited bacterial growth around the mold and concluded that the mold must have released some kind of antibacterial substance which stopped bacterial growth. In December 1945, he was awarded the Nobel Prize for his discovery (2).

Serendipity and "thinking outside the box", also boosted discoveries in cardiovascular (CV) medicine. The development of cardiac catheterization procedure is another fitting example. The first human practice of this technique is attributed to Werner Forssmann, who performed a catheterization of the right heart on himself and documented the successful endeavor by obtaining a chest X-ray showing the catheter located in the right atrium of his heart. Forssmann, who was initially severely rebuked by the head of his department for doing so, paved the way for modern catheterization techniques developed by Melvin Judkins and Andreas Grüntzig in the decades to come, and was also awarded the Nobel Prize years later (3).

However, as history shows, discoveries were often hindered by leading clinicians of their times who praised dogma over use of new, experimental techniques in clinical practice. For example, in the early 1960s, the Chair of Internal Medicine at the University of Zürich warned students about Swedish surgeon Åke Senning that "*this dangerous young man from Sweden (…) cuts into the heart without any of the respect for this organ (…)*", although Åke Senning was to become a pioneering cardiac surgeon (4).

Suppression of tumorigenicity 2 (ST2) in the field of immunity and heart failure (HF)

In the field of biomarker diagnostics, the protein "soluble suppression of tumorigenicity 2" (sST2) and its application in patients with HF is another example of serendipity. Over the last two decades, sST2 has attracted increasing scientific attention and was recognized as a biomarker for diagnosis and risk stratification of patients with HF, as recommended in the 2013 ACCF/AHA Guidelines for the Management of Heart Failure (5).

When sST2 was first discovered in 1989 in two laboratories investigating growth-stimulated fibroblasts, its functional properties remained largely unknown, despite its structural similarity to the interleukin-1 (IL-1) receptor (6). In fact, it took researchers until 2005 to identify IL-33

as the functional ligand for ST2L, the membrane-bound isoform of sST2 (7). IL-33 is released in response to cellular stress, inflammatory processes or apoptosis, consequently inducing protective measures in adjacent cells (8). sST2 is released in response to inflammatory cytokines, such as IL-1, IL-6 and tumor-necrosis factor alpha (TNFα) (9), binding to IL-33 and thusly attenuating cellular IL-33/ST2L signaling. The finding, that sST2 acts as a "decoy receptor" for IL-33, supported the hypothesis that ST2 elicits anti-inflammatory and immunomodulatory responses (10,11). However, a couple of years later, hemodynamic stress and strain to cardiomyocytes were identified as a second major trigger of sST2-secretion. This discovery led to multiple scientific investigations in the field of HF (12,13), CV diseases in general (14,15) and renal disease (16), which resulted in the current recommendation of the use of sST2 for the risk stratification of patients with HF.

Carbohydrate antigen 125 (CA125) in oncology and HF

Another example for serendipity in biomarker diagnostics is the application of CA125 in CV diseases. CA125 is a glycoprotein of the mucin protein family, which is released from the outer cell membrane after proteolytic cleavage. First described in ovarian cancer cell lines, CA125 has been used as a biomarker for therapy monitoring in ovarian cancer patients for decades (17,18). In other forms of malignant diseases, such as lung cancer, teratoma and non-Hodgkin's lymphoma (NHL) (19,20), elevated levels of CA125 have also been described. However, as CA125 is also secreted by pericardial and pleural tissues in response to stress, several publications reported elevated serum concentrations of CA125 in patients with decompensated HF (21,22). Furthermore, CA125 was recently associated with adverse outcomes in patients undergoing transcatheter aortic valve implantation (TAVI) (23,24). In fact, current research suggests that CA125 is also released by mesothelial cells in response to hemodynamic or inflammatory stimuli (25). Hence, CA125, which is broadly used in oncology, could offer additional diagnostic utility in patients with CV diseases.

The fact that CA125 has long been implemented in clinical practice offers advantages when compared to novel biomarkers. In fact, an important issue in biomarker diagnostics is applicability and reduction of costs. Laboratory analytics of novel protein-based biomarkers using assay systems done by hand, as performed in most clinical trials studying cardiac biomarkers, are time consuming, and require extensive technical and financial resources as well as personnel. These factors might hinder the more widespread use of novel biomarkers that have been discovered in translational research.

These issues can be easily circumvented when using laboratory markers such as CA125, as this biomarker is part of established routine diagnostic processes. Additionally, analysis using these biomarkers is considerably cheaper compared to cardiac biomarkers such as NT-proBNP (26).

Growth differentiation factor 15 (GDF15) in HF and adverse cardiac remodeling

GDF15 is a member of transforming growth factor-β superfamily member, which is an anti-inflammatory cytokine up-regulated locally with cardiac myocytes, activated mononuclear cells and released into the circulation (27). In physiological conditions the production of this cytokine is weak, consequently rather undetectable levels or lower concentrations of GDF15 can be identified in peripheral blood in healthy volunteers. The main stimuli for GDF15 synthesis and secretion are ischemia, hypoxia, inflammation, oxidative stress and injury (28). Elevated levels of GDF15 had been previously found in patients with HF, acute coronary syndrome/myocardial infarction (MI), atrial fibrillation/flutter, hypertrophic and dilated cardiomyopathy (29-32). Therefore, elevated levels of GDF15 were strongly associated with an increased rate of HF development. Recent clinical studies and several meta-analyses have shown significant association between high (>1,800 ng/L) GDF15 values and all-cause mortality, CV mortality, other vascular and nonvascular deaths, sudden cardiac death, bleeding death, HF manifestation, major adverse cardiac events (MACEs), and recurrent MI (33-35). Moreover, having higher predictive ability compared to high-sensitive cardiac troponins, C-reactive protein, galectin-3, and cystatin C the increased circulating levels of GDF15 have predicted mortality independently of conventional CV risk factors and yielded additional incremental value to NT-proBNP (35). Acute HF/acutely decompensated HF patients with GDF15 ≥3,000 ng/mL had about two-fold increased risk of death when compared with those who had GDF15 <3,000 ng/mL regardless of left ventricular ejection fraction (LVEF) (36). However, elevated levels of both GDF15 and BNP at discharge from hospital were associated with the 2-year mortality risk increased over four-fold. Although patients with HF with reduced

ejection fraction (HFrEF) had exhibited higher circulating levels of GDF15 when compared to patients with HF with medium reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF), GDF15 levels did not predict poor 1-year prognosis, but in combination with NT-proBNP significantly improves the discriminative accuracy of HF progression (36,37). Additionally, in the Danish-multinational monitoring of trends and determinants in cardiovascular disease (DAN-MONICA) study, serial measurements of the circulating levels of GDF15 have displayed only a slight improvement in the prognostication of the death due to coronary heart disease compared to a single measurement (38). Because there were no detectable associations between GDF15 levels and atherosclerotic CV disease events (37,38), GDF15 could be an useful biomarker for the identification of patients at risk for different causes of HF-related death and death due to bleeding including death associated with anticoagulation for atrial fibrillation. Probably multimarker approaches containing BNP and GDF15 might improve HF risk prediction at the general population and HF progression of individuals with established HF.

Conclusions

Serendipity and "thinking outside the box" is an opportunity for researchers to develop ideas and novel concepts, which can lead to interesting new discoveries for both diagnostics and drug development. As a researcher, one should keep an open mind to cross-discipline use of discoveries and observations in the journey from "bench to bedside".

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