Bringing Wearables from Bench to Bedside

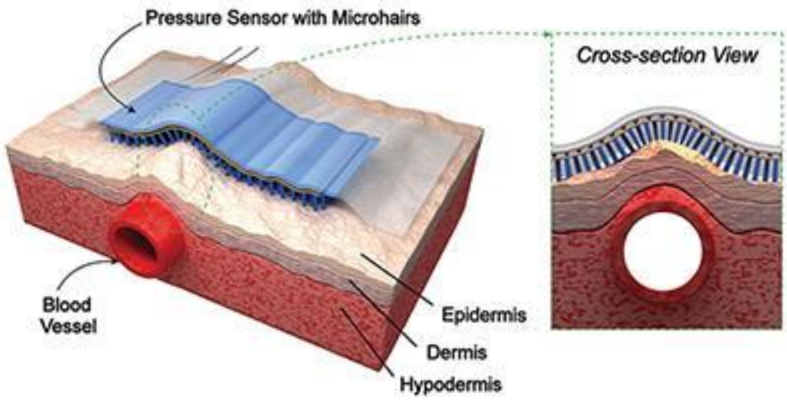
By Chibuike Uwakwe, an eWear-TCCI Science writer

Over 80 labs at Stanford University work on research that can be applied to the next generation of wearable technologies. From the intrinsically stretchable integrated circuits being developed in the lab of Prof. Zhenan Bao to proof-of-concept wearable devices and AI algorithms enabling insights using data from wearables, exciting research is being conducted at Stanford with the potential to revolutionize patient care. But how do innovative technologies developed in labs transform from proofs of concept to fully realized commercial medical devices? Professor Zhenan Bao's work fortunately offers an example of a model upon which this question might be answered.

A core goal of The Stanford Wearable Electronics Initiative (eWEAR) is to facilitate collaboration between Stanford researchers and industry, which is complemented by opportunities for inventors at the School of Engineering to connect with clinicians at the School of Medicine and identify critical use cases of new technologies. In Professor Zhenan Bao's case, a skin-like, wearable pressure sensor developed in her lab proved to be critical for addressing issues associated with the use of invasive arterial catheters in sick infants.

The journey from bench to bedside began with an innovation in the Bao Group involving a highly sensitive pressure sensor that interfaces intimately with the skin to easily measure physical data such as pulsations, blood pressure, and temperature. First, the Bao Group demonstrated the inexpensive fabrication of flexible, capacitive pressure sensors in their publication titled, "Highly sensitive flexible pressure sensors with microstructured rubber dielectric layers" [1]. They further showed that the sensors could be used to non-invasively monitor a continuous human radial artery pulse wave with high fidelity in their 2013 publication, "Flexible polymer transistors with high pressure sensitivity for application in electronic skin and health monitoring" [2].

Dr. Changhyun Pang, then a postdoc in the Bao Group, and his teammates aimed to make the wearable sensor as easy to fabricate as possible while incorporating the ability to remotely monitor the user. In their 2014 paper, Pang et al. shared a "Highly Skin-Conformal Microhairy Sensor for Pulse Signal Amplification" [3]. They successfully engineered an ultra-conformable capacitive pressure sensor that amplified weak pulsation signals from the human neck when attached like a bandage. The sensor device consisted of an upper multilayered component including the pressure sensor layer and a lower component featuring bio-inspired microhair structures to interface with the skin.



Highly skin conforming and pulse-detectable pressure sensor using micro-hair structures; Image credit: Bao Group, Stanford U.

This wearable pressure sensor was awe-inspiring for its potential to monitor cardiovascular and cardiac illnesses in new ways. However, it is at this stage of initial publication that many proof of concept technologies stall on their journey to the bedside. In seeking a partner to propel this wearable pressure sensor to the market, Professor Zhenan Bao was reintroduced to Xina Quan, Ph.D., who had prior experience leading the R&D division of several startup companies. Quan recognized how the pulse waveform measured by the wearable pressure sensor could be used to determine a user's blood pressure via algorithms, and she worked to develop the first wireless prototypes, spearheading several studies in adults to validate the technology.

In 2016, Bao and Quan spun-out the technology into PyrAmes Inc. as co-founders with a patent license obtained through Stanford's Office of Technology Licensing. When PyrAmes first started with Quan as CEO, she said it was most important to "understand how to get consistent and reproducible data." Quan and her team used machine learning techniques to develop algorithms for calculating blood pressure from pulse waveform data, optimized the structure and layout of the sensors in the device, and made the electrical components smaller and more power efficient. With a more robust device, Quan continued to lead validation studies moving from adult subjects aged 30 and older to pediatric subjects as young as 4 years old. It was the results of a study showing the high repeatability of pulse waveform measurements in pediatric subjects that sparked the interest of Dr. Anoop Rao, an Attending Neonatologist and Clinical Assistant Professor of Pediatrics at Stanford University School of Medicine, who believed that the wearable blood pressure sensor could be used to address an unmet need in neonatal critical care.

The standard practice for continuously measuring the blood pressure in neonates as small as 500g is to place an invasive arterial line, which involves inserting a needle and catheter into the wrist, foot or umbilicus of a baby. As one can imagine, this is a very painful procedure prone to error due to poor artery localization. What's more, arterial line placements can be time-intensive, skill-intensive, and cause clots that can limit the blood supply to a baby's limbs. With this in mind, Dr. Rao was eager to find a non-invasive way to continuously monitor a neonate's blood pressure.

After connecting with the team at PyrAmes, Dr. Rao led a study in collaboration with Quan to validate the sensor and machine learning algorithm in neonates at Lucile Packard Children's Hospital, "Clinical Study of Continuous Non-Invasive Blood Pressure Monitoring in Neonates," finding that the device could reliably measure blood pressure in critically ill term and preterm infants with various pathologies [4]. They soon after launched another multi-center study to assess the device's accuracy in anticipation of submission to the Food and Drug Administration (FDA) for 510(k) clearance. Indeed, the device, labeled Boppli®, was easy-to-use, accurate, and thoroughly validated.

Boppli® Platform; Image credit: PyrAmes Inc.

In September 2023, PyrAmes received FDA clearance for its Boppli® platform to continuously and non-invasively monitor the blood pressure of critically ill infants. To commercialize the device and bring it to neonatal intensive care teams across the United States, PyrAmes is currently conducting pilot evaluations at large Level III and IV neonatal intensive care units (NICUs).

PyrAmes received support from one of the early pioneers in the launch of the medical device industry, Thomas J. Fogarty. Dr. Fogarty, the Founder and Director of the Fogarty Institute for

Innovation said, “I can tell you firsthand the need for continuous non-invasive blood pressure monitoring to accelerate care decisions and improve the lives of almost every patient. Having spent three decades actively seeking solutions, I believe Pyrames has the potential to address this critical need.”

Dr. Anoop Rao expressed similar sentiments, “PyrAmes is at the cusp of establishing a new standard for BP measurement for neonates.” And when asked what excites her the most in regard to PyrAmes, Xina Quan said, “We have a device that can really make a difference.”

So, what’s next for PyrAmes? In the coming years, they plan to expand to maternal care, which would allow them to include outpatient markets. Long term, Quan says that PyrAmes will likely grow into the digital health space to integrate sophisticated diagnostics into their devices.

This journey from the bench to the bedside, or cradle in the case of Boppli, began with a key innovation and proof of concept created in a lab at the School of Engineering, which a physician at the School of Medicine identified as potentially useful for addressing an unmet need in medicine. Through this key collaboration, a novel device was developed and commercialized in a startup company to reach patients in the real world. The proximity of engineers and clinicians at Stanford University provides unique opportunities to engage in these types of collaborations, and eWEAR encourages and supports this process of bringing impactful wearable technologies to real people.

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