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INVENTION IS NOT AN OPTION

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Abstract

Inventors help solve all kinds of problems. The AAAS-Lemelson Invention Ambassador program celebrates inventors who have an impact on global challenges, making our communities and the globe better, one invention at a time. In this paper, we introduce two of these invention ambassadors: Dr. Suzie Pun and Dr. Juan Gilbert. Dr. Suzie Pun is the Robert F. Rushmer Professor of Bioengineering, an adjunct professor of chemical engineering, and a member of the Molecular Engineering and Sciences Institute at the University of Washington. Dr. Juan Gilbert is the Andrew Banks Family Preeminence Endowed Professor and chair of the Computer & Information Science & Engineering Department at the University of Florida. Both have a passion for solving problems and are dedicated to teaching their students to change the world.

Keywords

Invention; AAAS-Lemelson Invention Ambassador; Voting technology; Bioengineering; Materials science

INTRODUCTION

Inventors help solve all kinds of problems. The AAAS-Lemelson Invention Ambassador program celebrates inventors who have an impact on global challenges, making our communities and the globe better, one invention at a time.

We face many challenges. From figuring out how to save our planet to solving problems that impact only one country to making the quality of life better for many, inventors question the world around them, constantly looking for solutions. This article highlights the work of two academic inventors from very different fields whose inventions have made significant impact on society and solved challenging problems. Additionally, though many of us think of invention as an individual sport, the inventors highlighted in this article work collaboratively

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with their students in a university setting, using their positions as professors to not only do research and teach students but to help cultivate a new wave of future inventors.

Dr. Suzie Pun is the Robert F. Rushmer Professor of Bioengineering, an adjunct professor of chemical engineering, and a member of the Molecular Engineering and Sciences Institute at the University of Washington. Dr. Juan Gilbert is the Andrew Banks Family Preeminence Endowed Professor and chair of the Computer & Information Science & Engineering Department at the University of Florida. It is likely that neither had the career goal of becoming an inventor, but they both have a passion for solving problems and teaching their students one important lesson: “If it’s not the way you want it to be, change it.” And then they help their students do just that.

INVENTORS IN THE MAKING

Juan leads the Human-Experience Research Lab and has research projects in voting systems and technologies, advanced learning technologies, usability and accessibility, ethnocomputing (Culturally Relevant Computing), and databases/data mining. He holds one U.S. patent that has been licensed. He has published more than 180 articles and given more than 250 invited talks. He is an AAAS Fellow, an ACM Distinguished Scientist, an AAAS-Lemelson Invention Ambassador, a National Associate of the National Research Council of the National Academies, and a senior member of the IEEE.

One of the most impactful projects that Juan and his students have worked on is voting technology, where they created a universal voting technology that can accommodate all U.S. voters regardless of physical abilities or reading skills. They started with the premise that they could do something to remedy voting problems in the U.S. Believing that students are the future—and that their base of knowledge gave them both permission and a responsibility to change the world—the group took on “hanging chads.” The right to vote is a privilege of democracy and one that some groups have worked hard to obtain in the United States. Since each person wants to ensure that their vote counts, the 2000 elections brought to the forefront the worrying concern that our system does not always work as expected. Juan notes that in 2000, the State of Florida forever changed the future of voting in the U.S. As a result of the infamous hanging chads in the 2000 Presidential Election with Bush v. Gore, the U.S. Congress took action and passed the Help America Vote Act (HAVA) in 2002. The HAVA appropriated \$3.9 billion dollars for States to upgrade their voting equipment. HAVA also required that every voting place have at least one “accessible” voting machine. The aspiration for HAVA was to make voting more secure and accessible. However, there have been, and continue to be, issues in voting with respect to security and accessibility. As a result of the 2000 Presidential Election and the passing of the HAVA, Dr. Gilbert and his research team created Prime III, universal voting technology.

Suzie is a professor of bioengineering, an adjunct professor of chemical engineering, and a member of the Molecular Engineering and Sciences Institute at the University of Washington. Suzie once said she didn’t always see herself as an inventor, but she went after medical challenges with a vengeance, and, in the process, an inventor was born. She and her team focus on biomaterials and drug delivery, and she has contributed to drug delivery

vehicles that have entered clinical trials. Her research group has developed methods for drug delivery to the central nervous system as well as injectable, synthetic hemostats for trauma treatment. Like many academics, she has written many research articles (100+) and has given numerous presentations (100), but, in addition, she holds six patents. Suzie has been awarded a Presidential Early Career Award for Scientists and Engineers, a Young Investigator Award from the Controlled Release Society, the 2014 Inaugural Biomaterials Science Lectureship, and was named a Massachusetts Institute of Technology's TR100 Young Innovator and an American Institute for Medical and Biological Engineering fellow.

One of the major projects that Suzie and her group at the University of Washington have been working on for the last dozen years has been the development of synthetic polymers driven specifically by medical emergencies. Polymers, large molecules comprised of many smaller repeat units, have been broadly used in biomedical applications. Notable examples of polymers used in medicine include cellulose, a sugar-based polymer, used in kidney dialysis membranes; polyesters used in resorbable sutures; and polyacrylamides used in soft contact lenses. Suzie notes that the polymers that she and her group develop are bio-inspired and based on natural processes or naturally-occurring materials. Their materials integrate bioactive motifs with synthetic polymers. These bioactive motifs impart biological activity to the materials that remain amenable to large-scale production as synthetic polymers rather than as biologics, which carry high cost and challenges in scale-up. The team's technology development addresses medical needs using biological inspiration and design rationale. Two of her team's current projects are: PolySTAT, an injectable polymeric hemostat, and VIPER, a non-viral nucleic acid delivery vector.

DESCRIBING PRIME III

Prime III stands for premier third generation voting technology. First generation voting technologies are paper and pen, lever machines, and other physical voting apparatuses. Second generation would be touchscreen voting machines, also known as direct recording equipment (DRE). Third generation technologies are universally designed technologies. Universal design is the principle of designing a system or environment such that it has the broadest access for as many people as possible. Wheelchair ramps, for example, have a universal design because they can be used by people with wheelchairs and those who can walk. In 2002, when the HAVA was passed, conventional wisdom was that people with disabilities needed a separate voting machine. There was this notion that voters would have a separate but equal experience. It was thought that you could not build a universally designed voting machine. However, Dr. Gilbert and his team did just that—they built Prime III. In an interview, Dr. Gilbert said “So even if you can't see, you can't hear, you can't read, you don't have any arms, you can still vote on the same machine as everyone else” (1).

Prime III allows voters to mark their ballots using touch and/or voice. Voters can interact with the system by touch or a button switch and/or by voice through a headset with a microphone. These interactions allow people who can't see, hear, or read and those with limited upper body mobility to all privately and independently mark their ballots on the same machine as everyone else. Independent of your ability or disability, everyone can use the same technology to mark their ballots using Prime III. The first version of Prime III was

created in 2003 (Figure 1). Dr. Gilbert and his team didn't know it at the time, but they had created the world's most accessible voting technology, and they would forever change voting in the U.S.

Since 2003, Dr. Gilbert and his team have conducted numerous elections, research studies, and demonstrations all across the U.S. Oregon, Wisconsin, and New Hampshire have all done pilot elections using Prime III. Prime III has also been used in organizational elections for Self-Advocates Becoming Empowered, National Council of Independent Living, National Society of Black Engineers, and others. Prime III was even used in an elementary school to do a Presidential mock election. Prime III has been used by people with disabilities ranging from visual impairments to missing limbs as well as people who do not have any disabilities. In all of these studies, there were insights gained into how universal design can be implemented in voting. As such, Prime III has been tested and proven to be a universally designed voting technology.

In 2015, Dr. Gilbert released Prime III as open source on GitHub. The State of New Hampshire acquired Prime III and used it statewide in 2016 in the February Presidential Primaries. New Hampshire was the first state to adopt Prime III for statewide use. However, several others are investigating Prime III as well. One of the motivating factors for adopting Prime III is that the HAVA funding has run out, and there's no promise of additional funding. Therefore, states are looking for options to replace their decaying voting technologies. As an open source option, the cost savings are significant.

In addition to being an accessible voting tool that implements a universal design, Prime III is also secure, an element more important than ever in light of recent events. While election security has always been a major concern, in the recent 2016 U.S. Presidential Election, election security surged to the forefront of many discussions. Questions about the security of votes were prominent, with candidates and pundits questioning the integrity of the system. Furthermore, there were several hacking incidents on mail servers and other computers that fed the fears of elections being hacked. Prime III's major advantage in this respect is that the software is independent (2). Software-independent voting technologies have the property that no intentional or unintentional change in the software can cause an undetected change in the outcome of the election. When a voter uses Prime III, they will mark their ballot using the universal design features. When they are done, Prime III prints a paper ballot with their selections. As such, the paper ballot is the ballot of record. Prime III doesn't retain any information about the voter or their selections. In many respects, Prime III is a sophisticated ink pen. Therefore, changing the software cannot alter votes because the printed ballot is the actual ballot of record.

Prime III was created at a time when conventional wisdom was that people with disabilities needed a separate voting machine. The timing and impact of this invention was way ahead of society. Fast-forward to the current time, and voting machine manufacturers are creating universally designed voting machines inspired by Prime III, and elections officials and voters alike are requesting these technologies. More than a decade after its initial creation, Prime III has gone prime time in statewide elections in New Hampshire. In the years to

come, many will realize that Dr. Gilbert's invention forever changed the landscape of voting in the U.S.

UNDERSTANDING PolySTAT AND VIPER

PolySTAT: An Injectable Polymeric Hemostat

Trauma is one of the major causes of death in young people in the United States. Of the trauma-related deaths, about one-third are due to hemorrhage, or uncontrolled bleeding, that occurs immediately following the injury (3,4). Direct methods, such as compression and tourniquet application, are used in the field to minimize blood loss. To restore blood loss during resuscitation, patients are infused with human plasma or blood products or other intravenous fluids (5). However, there remains a great need for injectable therapies that can be administered by first responders to rapidly halt bleeding at incompressible injury sites.

Suzie's team partnered with Dr. Nathan White and his laboratory to develop injectable hemostatic polymers for use in trauma medicine. The design of the first polymer they developed, PolySTAT (**polymeric hemostat**), was inspired by the actions of Factor XIII, an enzyme that, when activated, crosslinks and stabilizes fibrin, the protein used to form the mesh in blood clots. In addition to its biological activity, they wanted a material that would not require special storage conditions so that it could be easily transported and used by first responders. The list of their desired material characteristics and proposed design solutions is shown in Table 1.

Using a recently developed controlled polymerization technique known as RAFT (reversible addition-fragmentation chain transfer) polymerization, they synthesized the first generation PolySTAT, a polymer that displays on average 16 fibrin-binding peptides on a water-soluble polymer backbone (6). PolySTAT integrates into forming clots (Figure 2), resulting in a hybrid clot comprising natural fibrin protein as well as synthetic PolySTAT. The hybrid clot shows greater strength and more resistance to degradation under coagulopathic conditions that often result in patients after traumatic injury.

PolySTAT was designed to circulate for around one hour after administration; this parameter was selected because ~85% of the United States population has access to a trauma center via ambulance or helicopter within 60 minutes (7). Over time, PolySTAT is eliminated through the urine to minimize risk of thrombosis. PolySTAT was tested in a rat femoral artery injury model with fluid resuscitation. Whereas untreated animals or animals treated with control substances (e.g., albumin as an oncotic control or a comparable control polymer displaying scrambled peptides that do not bind to fibrin) had only 0% to 40% survival, 100% of animals treated with PolySTAT survived the time course of the study. Furthermore, PolySTAT-treated rats had significantly less blood loss compared to all other control groups (6). These results suggest that PolySTAT is able recognize injury sites after intravenous injection and help to stop bleeding and increase survival rate in this animal model of trauma.

In addition to use as an injectable hemostat, PolySTAT could be used in wound dressings to improve the activity of hemostatic gauze. Therefore, Suzie's team also partnered with Dr. Tae Hee Kim's group at the Korean Institute of Industrial Technology to integrate PolySTAT

into chitosan gauze. Compared to commercially available chitosan gauze, their PolySTAT-imbued gauze showed improved efficacy in the rat femoral artery injury model; animals treated with the PolySTAT/chitosan gauze lost less blood and required less fluid resuscitation compared to animals treated with the commercially available gauze (8).

VIPER: A Non-Viral Nucleic Acid Delivery Vector

Suzie and her team also work on VIPER, a non-viral nucleic acid delivery vector. Nucleic acids are a relatively new class of drugs and include oligonucleotides (such as Vitravene, an anti-viral drug that is FDA-approved for treatment of cytomegalovirus retinitis), small-interfering RNA, messenger RNA, and gene therapies (such as Glybera, the first gene medicine approved for use in Europe and used to treat lipoprotein lipase deficiency). A major challenge in clinical translation of gene therapies is efficient and safe delivery, a process called “transfection.” The delivery technologies for nucleic acid drugs can be categorized into two main technology groups: viral vectors and non-viral vectors. Viral vectors are engineered viruses altered to minimize pathogenicity and insert instead therapeutic genes. Viral vectors tend to be highly efficient at gene transfer but have challenges related to safety and high cost of large scale manufacture (9). In contrast, non-viral vectors, such as lipids and polymers, offer advantages in safety and production cost but are typically much lower in delivery efficiency, especially in complex living organisms (10).

One of the critical steps in achieving efficient non-viral gene transfer is endosomal escape. Both viral and non-viral vectors are taken up into the mammalian cell via lipid-membrane encapsulated vesicles called endosomes. These endosomes ferry cargo to the lysosomes, often described as the ‘garbage disposal and recycling centers’ of cells. Thus, without efficient escape from the endosomes, the nucleic acid drugs carried by these vectors are neutralized and degraded within the lysosomes. However, endosomal escape requires selective disruption of the endosome membrane without affecting the cell membrane, which has a similar composition; disruption of the cell membrane would result in toxicity to the cell.

In order to develop a synthetic delivery vector with efficient and selective endosomal membrane disruption ability, Suzie’s team designed a material that mimics the endosomal escape strategy employed by adenovirus. Adenovirus contains a membrane-active protein called protein VI that is hidden by the virus protein shell until the virus is taken into the host cell. There, the virus protein shell rearranges and exposes protein VI, which then interacts with the endosomal membrane to facilitate release of the virus from the endosome. They therefore designed a polymer, called VIPER (Virus-Inspired Polymer for Endosomal Release), that similarly masks a membrane-active peptide. Upon sensing the endosomal environment, the polymer complex rearranges to expose the peptide, resulting in endosomal membrane destabilization and cargo release from the vesicle (11).

VIPER, also synthesized by RAFT polymerization, contains two segments (Figure 3A). The first block, shown in green, is hydrophilic, or water-loving, and also positively charged for binding nucleic acid cargo. The second block, shown in pink, is hydrophobic, or water-hating, at physiological pH (pH 7.4) but that becomes hydrophilic at acidic pH (e.g., pH < 6.0). The second block is grafted with a bee venom peptide called melittin (shown as the

yellow and black-striped triangle). Melittin disrupts lipid membranes and has been shown to improve gene delivery when conjugated to polymer carriers, but at the cost of cell survival (12–14).

The hydrophobic sections of VIPER therefore drive self-assembly of the polymer at pH 7.4 into nanoparticles that hide both the hydrophobic polymer blocks and the membrane-disruptive melittin peptides. After entry into the cell, the VIPER nanoparticles containing gene therapies are exposed to the acidic endosomal environment. In response to the environmental change that occurs after cell uptake, VIPER switches characteristics, resulting in a conformational change that exposes the melittin peptide and disrupts endosomes to release VIPER and cargo to the cell cytoplasm (Figure 3B). They have shown that gene-loaded VIPER complexes are selectively membrane-disruptive in acidic environments and that these VIPER complexes are able to efficiently escape endosomes after cell entry in contrast to control polymers that lack the melittin peptide (11).

VIPER is their most potent gene transfer material to date, outperforming commercially available reagents in gene transfer to cultured cells. They have demonstrated that the transfection efficiency in cultured cells ranges from ~20% for difficult-to-transfect stem cells to over 90% for certain rapidly-dividing cancer cell lines. Importantly, the team demonstrated successful gene transfer to both tumors and to the brain in animal models. They are moving forward now to use VIPER for therapeutic gene transfer in a variety of disease applications, both in their laboratory and in collaboration with other academic groups and industry.

CONCLUSION

While the inventions of Suzie Pun and Juan Gilbert are worlds apart, there are some important truths in the world of inventors. First, inventors can and do come from a variety of backgrounds—different fields, geographic locations, ages, genders, ethnicities, and racial groups. Second, it appears that the first thought of would-be inventors is not, “How do I become an inventor?” Instead, it is, “How do I solve this problem?” Third, teamwork is an important part of the solution. Teaming with students, fellow researchers, problem-solvers, and people with different types of expertise seems to be a prerequisite for success. Fourth, there is a “can do” attitude that turns failures into successes and challenges into opportunities and possibilities. Lastly, there is passion and dedication to making people’s lives better.

Seek out inventors in your communities and at your institutions—they can show you how they are trying to change the world and how much they believe that invention is not an option.

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Figure 1.
Prime III, a secure, accessible voting system.

Figure 2.

Confocal images of fibrin (red) clots formed in the presence of polySTAT (green) that polySTAT is integrated throughout the fibrin network. Scalebar = 10 μ m. Figure reproduced with permission from AAAS (Chan LW, Wang X, Wei H, Pozzo LD, White NJ, Pun SH. A synthetic fibrin cross-linking polymer for modulating clot properties and inducing hemostasis. *Sci Transl Med.* 7(277): 277ra29-77ra29; 2015), copyright 2015.

Figure 3.

(A) Schematic of VIPER and chemical structure of VIPER. (B) Mechanism of VIPER assembly, cellular uptake and endosomal escape. See text for detailed explanation. Figure reproduced with permission from Wiley (11. Cheng Y, Yumul RC, Pun SH. Virus-inspired polymer for efficient in vitro and in vivo gene delivery. *Angew Chem.* 128(39): 12192-12196; 2016.), copyright 2016.

Table 1

Design Characteristics and Proposed Design Solutions Used During Development of PolySTAT

Desired Characteristic		Design Solution
Bioactivity	Specific clot recognition	Peptide that binds fibrin but not fibrinogen
	Crosslinks clots	Multivalent display of fibrin-binding peptide on polymer backbone
	Access internal injury sites	Injectable, water-soluble polymer
	Clears out of the body a few hours after injection	Molecular weight ~40–60 kDa
Production	Affordable and reproducible large-scale production	Synthesis by controlled living polymerization techniques
	Does not require cold storage	Completely synthetic material; avoid protein components