The Applied Innovation Review (AIR) is an on-line and in-print publication on special topics in Technology Business Innovation, New Venture Models and Education in Entrepreneurship and Innovation. Unlike traditional business reviews, papers in AIR identify more current research, best practices and trends that can affect the global economy.

Information in AIR is intended to be effective, modern in style, insightful and useful for industry, policy makers and educators interested in participating in entrepreneurship & innovation. AIR papers and opinions may preview work still in formation and that may be accepted by more formal journals at a later time.

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Table of Contents

Letter from SCET Founding Director and Chief Scientist .................4
BlockChain Technology: Beyond Bitcoin ........................................6
Saving the Planet: The Market for Sustainable Meat Alternatives .......20
3D Printing Standards and Verification Services ...............................34
A Novel Approach for Preventing Neurological Disease Associated with Blood-Brain Barrier Pathology ........................................45
A Student-Centered Approach and Mindset-Focused Pedagogical Approach for Entrepreneurship and Leadership .................. 57
June, 2016.

Dear Global Innovation Community,

On behalf of the Sutardja Center for Entrepreneurship and Technology at UC Berkeley, it is my pleasure to bring to you the second edition of the Applied Innovation Review (AIR).

We have come a long way since we decided the focus of the inaugural version of AIR in 2015. Last year, our community of scholars, innovators and entrepreneurs was trying to understand the potential of Self-Driving Vehicle Strategies, the Technology Effects on Banking, the Intersection between Technology and Global Inclusion, and the Berkeley Method of Entrepreneurship.

This year, the selection of the topics for the Applied Innovation Review has been supported by the introduction of one of our new What’s Next Watchlist. The Watchlist is a framework that was created by tracking applied research projects and venture investment with the aim to determine which emerging areas are the best investment bets for the present year, based both on their timing and their potential impact.

The Watchlist was obtained by tracking two sources of data. One is the technical reports of UC Berkeley’s Sutardja Center projects. Authors represent Silicon Valley Executives, Ph.D. students, and undergraduates. The second source is from the Series A investments over the past 12 months from leading VC firms established in the Bay Area and around the United States. While some of our results were evident since the beginning, such as the current importance of Cybersecurity and Encryption, or the news ways in which Big Data has been able to blend into the Healthcare industry, others consolidated their places at the top of the list just recently given the different development stages of their own markets. These included the potential of Drones and Robotics, Blockchain Technology, and the new ways in which media manages to interact and make content accessible for consumer brands and retail.

What’s Next Watchlist — Emerging Areas to Watch for 2016:

Healthcare + Data / Cognitive Technology
Cybersecurity and Encryption
Data + Cognitive Technology + Enterprise
Drones and Robotics
Connected Cars
3D Printing, Digital Manufacturing, and Verification
Fintech, Transactions, and Blockchain
Education and Training + IT/Data
Collaboration, Workspace, possibly with Virtual Reality
Media + Brands + Retail and Data / Cognitive Technology

Influenced by the 2016 Watchlist, the focus of this year’s issue turns to explore the disruption potential of Blockchain Technology, the promise of the Market for Sustainable Meat Alternatives, the emergence of 3D Printing Standards and Services, the ability to Prevent Neurological Diseases such as dementia and epilepsy, and a Novel Approach into reshaping Leadership and Entrepreneurship.

As you browse through AIR’s pages, we hope you are as excited as we were when putting its pieces together, and realize how far we have come in improving society through the technological development, entrepreneurship, and innovation.

Sincerely,

Ikhlaq Sidhu

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BlockChain Technology: Beyond Bitcoin

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Abstract

A blockchain is essentially a distributed database of records, or public ledger of all transactions or digital events that have been executed and shared among participating parties. Each transaction in the public ledger is verified by consensus of a majority of the participants in the system. Once entered, information can never be erased. The blockchain contains a certain and verifiable record of every single transaction ever made. Bitcoin, the decentralized peer-to-peer digital currency, is the most popular example that uses blockchain technology. The digital currency bitcoin itself is highly controversial but the underlying blockchain technology has worked flawlessly and found wide range of applications in both financial and non-financial world.

The main hypothesis is that the blockchain establishes a system of creating a distributed consensus in the digital online world. This allows participating entities to know for certain that a digital event happened by creating an irrefutable record in a public ledger. It opens the door for developing a democratic open and scalable digital economy from a centralized one. There are tremendous opportunities in this disruptive technology, and the revolution in this space has just begun.

This white paper describes blockchain technology and some compelling specific applications in both financial and non-financial sector. We then look at the challenges ahead and business opportunities in this fundamental technology that is all set to revolutionize our digital world.
Introduction

A blockchain is essentially a distributed database of records, or public ledger of all transactions or digital events that have been executed and shared among participating parties. Each transaction in the public ledger is verified by consensus of a majority of the participants in the system. Once entered, information can never be erased. The blockchain contains a certain and verifiable record of every single transaction ever made. To use a basic analogy, it is easier to steal a cookie from a cookie jar, kept in a secluded place, than to steal the cookie from a cookie jar kept in a market place, being observed by thousands of people.

Bitcoin is the most popular example that is intrinsically tied to blockchain technology. It is also the most controversial one since it helps to enable a multibillion-dollar global market of anonymous transactions without any governmental control. Hence it has to deal with a number of regulatory issues involving national governments and financial institutions.

However, Blockchain technology itself is non-controversial and has worked flawlessly over the years and is being successfully applied to both financial and non-financial world applications. Last year, Michael Ivy, the co-founder of a California public relations firm, noted here that even Bitcoin is not going anywhere.

Financing institutions and banks no longer see blockchain technology as a threat to traditional business models. The world’s biggest banks are in fact looking for opportunities in this area by doing research on innovative blockchain applications.

Section I: BlockChain Technology

1. Short History of Bitcoin

In 2008, an individual (or group) writing under the name of Satoshi Nakamoto published a paper entitled “Bitcoin: A Peer-To-Peer Electronic Cash System”. This paper described a peer-to-peer version of the electronic cash that would allow online payments to be sent directly from one party to another without going through a financial institution. Bitcoin was the first realization of this concept. Now “cryptocurrencies” are the term that is used to describe all networks and mediums of exchange that uses cryptography to secure transactions as against those systems where the transactions are channelled through a centralized trusted entity.

The author of the first paper wanted to remain anonymous and hence no one knows Satoshi Nakamoto to this day. A few months later, an open source program implementing the new protocol was released, beginning with the Genesis block of Internet commerce is exclusively tied to the financial institutions serving as the trusted third party who process and mediate any electronic transaction. The role of trusted third party is validate, safeguard and preserve transactions. A certain percentage of fraud is unavoidable in online transactions and that needs mediation by financial transactions. This results in high transaction costs.

Bitcoin uses cryptographic proof instead of the trust-in-the-third-party mechanism for two willing parties to execute an online transaction over the Internet. Each transaction is protected through a digital signature, is sent to the “public key” of the receiver, and is digitally signed using the "private key" of the sender. In order to spend money, the owner of the cryptocurrency needs to prove his ownership of the "private key".

Applied Innovation Review

Issue No. 2 June 2016

August 10

August 11

September 9

September 12

January 9

January 12

Figure 1: The History of Bitcoin

Figure 2: Traditional Online Financial Transactions using third party trust (e.g., PayPal, etc.)
The entity receiving the digital currency then verifies the digital signature, which implies ownership of the corresponding “private key”, by using the “public key” of the sender on the respective transaction.

Each transaction is broadcasted to every node in the Bitcoin network and is then recorded in a public ledger after verification. Every single transaction needs to be verified for validity before it is recorded in the public ledger. The verifying node needs to ensure two things before recording any transaction:

1. Spender owns the cryptocurrency, through the digital signature verification on the transaction.

2. Spender has sufficient cryptocurrency in his account, through checking every transaction against the spender’s account, through checking every transaction against the spender’s account, or “public key”, that is registered in the ledger. This ensures that there is sufficient balance in his account before finalizing the transaction.

However, there is question of maintaining the order of these transactions that are broadcasted to every other node in the Bitcoin peer-to-peer network. The transactions do not come in order in which they are generated, and hence there is a need for a system to make sure that double-spending of the cryptocurrency does not occur. Considering that the transactions are passed node by node through the Bitcoin network, there is no guarantee that orders in which they are received at a node are the same order in which these transactions were generated. The above means that there is a need to develop a mechanism so that the entire Bitcoin network can agree regarding the order of transactions, which is a daunting task in a distributed system.

The Bitcoin solved this problem by a mechanism that is now popularly known as Blockchain technology. The Bitcoin system orders transactions by placing them in groups called blocks and then linking these blocks through what is called Blockchain. The transactions in one block are considered to have happened at the same time. These blocks are linked to each other (like a chain) in a proper linear, chronological order with every block containing the hash of the previous block.

There still remains one more problem: Any node in the network can collect unconfirmed transactions and create a block and then broadcast it to the rest of the network as a suggestion as to which block should be the next one in the blockchain. How does the network decide which block should be next in the blockchain? There can be multiple blocks created by different nodes at the same time. One can’t rely on the order since blocks can arrive at different orders at different points in the network.

Bitcoin solves this problem by introducing a mathematical puzzle: each block will be accepted in the blockchain provided it contains an answer to a very special mathematical problem. This is also known as “proof of work”: a node generating a block needs to prove that it has put enough computing resources to solve a mathematical puzzle. For instance, a node can be required to find a “nonce” which when hashed with both transactions and hashes of previous blocks produces a hash with a certain number of leading zeros.

The average effort required is exponential in the number of zero bits required but verification process is very simple and can be done by executing a single hash.
There is a race to validate transactions in the blockchain. Figure 6 shows the race between two nodes in the Bitcoin network to validate a transaction. The first node to solve the mathematical puzzle and generate a block is awarded the transaction fees and a reward.

The network only accepts the block generated by the first node to solve the puzzle. This ensures that only one block will be generated in a given time interval. The nodes that do not win the race cannot compete with the first node to validate the block. Thus, the race is not a competition between miners but rather a competition between nodes to validate transactions.

Companies like IBM, Samsung, Overstock, Amazon, USB, Citi, eBay, and Verizon Wireless have recently joined forces with the New York based financial technology firm R3 in September 2015 in order to create a framework for using the blockchain technology in the financial market. This is the first time banks have come to work together to find applications of blockchain technology.
and attract investors. The stock exchanges list company shares for secondary market to function securely with trades settling and clearing in a timely manner. It is now theoretically possible for companies to directly issue the shares via the blockchain. These shares can then be purchased and sold in a secondary market that sits on top of the blockchain. Here are some examples:

**NASdaq Private Equity**

NASdaq launched its Private Equity exchange in 2014. This is meant to provide the key functionalities like Cap table and investor relationship management for the the pre-IPO or private companies. The current process of trading stocks in this exchange is inefficient due to involvement of multiple 3rd parties. NASDAQ has joined hands with a San Francisco based Startup called chain.com to implement private equity exchange on top of Blockchain. Chain.com is implementing Blockchain based smart contracts to implement exchange functionality. This product is expected to be fast, traceable and efficient.

**Medici** is being developed as a securities exchange that uses the Counterparty implementations of Bitcoin 2.0. The goal here is to create a cutout for secondary market trading. Medici is an open source project with focus on Side-chains to avoid fragmentation, security and other issues related to alternative cryptocurrencies. Uses can range from registering securities, such as stocks, bonds and derivatives, to securing bank balances and mortgages.

**CoInsters** is a New York based bitcoin exchange. It is working on a Project Highline, a method of using the blockchain to settle and clear financial transactions in T+10 minutes rather than the customary T+3 or T+2 days. Despite their popularity, CoInsters is a decentralized prediction market that will allow users to buy and sell shares in anticipation of an event with the probability that a specific outcome occurs. This can also be used to make financial and economic forecasts based on the “wisdom of crowds”.

**Bitshares** are digital tokens that reside in the blockchain and reference specific assets such as currencies or commodities. The Token holders may have the unique feature of earning interest on commodities, such as gold, and oil, as well as dollars, euros and currency instruments.

### 1.2 Insurance

Assets which can be uniquely identified by one or more identifiers that are difficult to destroy or replicate can be registered in blockchain. This can be used to verify ownership of an asset and also track the transaction history. Any property (physical or digital such as real estate, automobiles, physical assets, laptops, other valuables) can potentially be registered in blockchain and the ownership, transaction history can be validated by anyone, especially insurers.

**Everledger** is a company which creates permanent ledger of diamond certification and the transaction history of the diamond using blockchain. The characteristics which uniquely identify the diamond such as height, width, depth, color etc are hashed and registered in the ledger. The verification of diamonds can be done by insurance companies, law enforcement agencies, owners and claimants. Everledger provides a simple to use web service API for looking at a diamond, and create, read or update claims by insurer and to the outcome for police reports on diamonds.

### 2. Non-Financial Applications: 2.1 Notary Public

Verifying authenticity of the document can be done using blockchain and eliminates the need for centralization or reliance on central authority. The document certification service helps in Proof of Ownership (who authored it), Proof of Existence (at a certain time) and Proof of Integrity (not tampered) of the documents. Since it is counterfeit-proof and can be verified by independent third parties, these services are legally binding. Using blockchain for notarization secures the privacy of the document as well as those who seek certification. By publishing proof of publication using cryptographic hashes of files into blockchain takes the notary timestamping to a new level. Using blockchain technology also eliminates the need for expensive notarization fees and ineffective ways of transferring documents.

**Stampery** is a company which can stamp email or any files using blockchain. It simplifies certifying of emails by just emailing them to an email specifically created for each customer. Law firms are using Stampery’s technology for a very cost effective way to certify documents.

**Viarion** is one of the companies which uses clearinghouse protocol for notary service. Viarion is a New York based bitcoin exchange. It is working on a Project Highline, a method of using the blockchain to settle and clear financial transactions in T+10 minutes rather than the customary T+3 or T+2 days.

### 2.2 Applications of Blockchain in the Music Industry

The music industry has gone a big change in last decade due to the growth of Internet and availability of a number of streaming services over the Internet. This change is impacting everyone in the music industry: artists, labels, publishers, songwriters and streaming service providers. The process by which music royalties are determined has always been a convoluted one, but the emergence of the Internet has made it even more complex giving rise to the demand of transparency in the royalty payments by both artists and songwriters.

This is where the blockchain can play a role. The technology can help maintain a comprehensive and accurate distributed database of music rights ownership information in a public ledger. In addition to rights ownership information, the royalty split for each work, as determined by Smart Contracts, could be added to the database. This Smart Contracts would in turn define the relationship between different stakeholders (addressess) and automate their interactions.

### 2.3 Decentralized proof of existence of documents

Validating the existence or the possession of signed documents is very important in any legal solution. The traditional document validation models rely on central authorities for storing and validating the documents, which presents some obvious security challenges. These models become even more difficult as the documents become older.

The blockchain technology provides an alternative model to proof-of-existence and possession of legal documents. Proof of Existence is a simple service that allows one to anonymously and securely store online proof of existence of any document. This service simply stores the cryptographic digest of the file, linked to the time in which a user submits his document. It is worth noting that the cryptographic digest or fingerprint is what is stored, not the actual document. In this way, the user does not need to worry about the privacy aspect and protecting his information.

This allows then a user to later certify the existence of a document that existed at a certain time.

By leveraging the blockchain, a user can simply store the signature and timestamp associated with a legal document in the blockchain and validate it anytime using native blockchain mechanisms.

The major advantages of this service is security and privacy that allow a user to give decentralized proof of the document that can’t be modified by a third party. The existence of the document is validated using blockchain that does not depend on a single centralized entity. Proof of Existence web service is available at [https://proofofexistence.com](https://proofofexistence.com/).

### 2.4 Decentralized Storage

Cloud file storage solutions such as Dropbox, Google Drive or OneDrive are growing in popularity to store documents, photos, video and music files. Despite their popularity, cloud file storage solutions typically face challenges in areas such as security, privacy and data control. The major issue is that one has to trust a third party with one’s confidential files.

**Storj** provides a blockchain based peer-to-peer distributed cloud storage platform (see Appendix for detailed description) that allows users to transfer and share data without relying on a third party data provider. This allows people to share unused internet bandwidth and spare disk space in their personal computing devices to those looking to store large files in return for bitcoin based micropayments.

Absence of a central control eliminates most traditional data failures and outages, as well as significant increasing security, privacy and data control. Storj’s platform depends upon a challenge algorithm to offer incentivization for users to properly participate in this network.
2.5 Decentralized IoT

The Internet of Things (IoT) is increasingly becoming a popular technology in both the consumer and the enterprise space. A vast majority of IoT platforms are based on a centralized model in which a broker or hub controls the interaction between devices. However, this approach has become impractical for many scenarios in which devices need to exchange data between themselves autonomously. This specific requirement has lead to efforts towards decentralized IoT platforms.

The blockchain technology facilitates the implementation of decentralized IoT platforms such as secured and trusted data exchange as well as record keeping. In such an architecture, the blockchain serves as the general ledger, keeping a trusted record of all the messages exchanged between smart devices in a decentralized IoT topology.

IBM, in partnership with Samsung, has developed a platform ADEPT (Autonomous Decentralized Peer To Peer Telemetry) that uses elements of the bitcoiin’s underlying design to build a distributed network of devices, or decentralized Internet of Things (IoT). ADEPT uses three protocols in the platform: BitTorrent (file sharing), Ethereum (Smart Contracts) and TeleHash (Peer-To-Peer Messaging).

In this example, Bitcoin-based micro-payments serve as both an incentive and method of payment while a separate blockchain is used as a datastore for file metadata.

2.6 Blockchain-based Anti-Counterfeit Solutions

Counterfeiting is one of the biggest challenges in modern commerce. In particular, it is one of the biggest challenges that digital commerce world faces today. Existing solutions are based on reliance on trust on a third party trusted entity that introduces a logical friction between merchants and consumers.

The blockchain technology, with its decentralized implementation and security capabilities, provides an alternative to existing anti-counterfeiting mechanisms. One can envision a scenario in which brands, merchants and marketplaces are part of a blockchain network with nodes storing information to validate the authenticity of the products. With the use of this technology, stakeholders in the supply chain need not rely on a centralized entity for authenticity of the branded products.

BlockVerify provides blockchain based anti-counterfeit solutions that introduce transparency to supply chains. It is finding applications in the pharmaceutical, luxury items, diamonds and electronics industries.

2.7 Internet Applications

Namecoin is an alternative blockchain technology (with small variations) that is used to implement a decentralized version of Domain Name Server (DNS) that is resilient to censorship. Current DNS servers are controlled by governments and large corporations, and could abuse their power to censor, hijack, or sny on a consumer’s Internet usage.

With Blockchain technology Internet’s DNS or phonebook is maintained in a decentralized manner and every user can have the same phone book data on their computer. Public Key Infrastructure (PKI) technology is widely used for centralized digital certificate management of digital certificates. Every device needs to have root certificate of the Certification Authority (CA) to verify digital signature. While PKI has been widely deployed and incredibly successful, dependence on a CA makes scalability an issue.

The characteristics of the Blockchain can help address some of the limitations of the PKI by using Keyless Security Infrastructure (KSI). KSI uses cryptographic hash functions, allowing verification to rely only on the security of hash functions and the availability of a blockchain.

Section IV: Risks of Adoption

Blockchain is a promising breakthrough technology. As we described before, there are vast array of applications or problems that can be solved using Blockchain based technology, spanning from Financial (remittance to investment banking) to non-financial applications like Notary services.

Most of these are radical innovations. As it happens with the adoption of radical innovations, there are significant risks of adoption.

Behavior change: Change is constant, but there is resistance to change. In the world of non-trustable trusted third parties introduced by Blockchain, customers need to get used to the fact that their electronic transactions are safe, secured and complete. The present day intermediaries like Visa or Mastercard (in case of a credit card) will also go through a change of roles and responsibilities. We envision that these companies will also invest and move their platforms to be Blockchain-based. They will continue to provide services to further customer relationship.

Scaling: Scaling of the current services based on Blockchain presents a challenge. Imagine yourself executing a Blockchain transaction for the first time. You will have to go through downloading the entire set of existing Blockchain and validate before executing your first transaction. This may take hours or longer as the number of blocks increase exponentially.

Bootstrapping: Moving the existing contracts and smart contract frameworks to the new Blockchain based methodology presents a significant set of migration tasks that need to be executed. For example, in case of Real Estate ownerships, the existing documents lying in County or Escrow companies need to be migrated to the equivalent Blockchain form. This may involve time and costs.

Government Regulations: In the new world of Blockchain-based transactions, government agencies like FTC and SEC may slow down the adoption by introducing new laws to monitor and regulate the industry for compliance. In a way, this may help adoption in the United States by strengthening customer trust. In more controlled economies like China, the adoption will face significant headwinds.

Fraudulent Activities: Given the pseudonymous nature of Blockchain transactions, coupled with ease of moving valuables, the “bad guy” may misuse the technology for fraudulent activities like money trafficking. That said, with enough regulations and technology-support, law enforcement agencies will be able to monitor and prosecute these individuals.

Quantum Computing: The basis of Blockchain technology relies on the very fact that it is mathematically impossible for a single party to game the system due to lack of needed compute power. But with the future advent of Quantum Computers, the cryptographic keys may be easy enough to crack within a reasonable time through a sheer brute force approach. This would bring the whole system to its knees.

The counter-argument would be for keys to become even stronger so that they may not be easy to crack.

Section V: Corporate Funding & Interest

In 2015, the bitcoin currency has reached yearly highs in both volume and price over the course of September-October. The digital currency is gaining traction both in the consumer marketplace as a tradeable security, as well as with regulators. It isn’t just digital-currency enthusiasts that are bullish; equity research firm Wedbush expects it to rise to $600 because of its growing adoption.

This enthusiasm may be because of the large quantities of capital being invested into the digital infrastructure. Excitement grows as Bitcoin and blockchain firms have received a record US$1 Billion in investment as 2015 came to an end. American Express, Bain Capital, Deloitte, Goldman Sachs, MasterCard, the New York Life Insurance Company, the New York Stock Exchange and all of them have poured millions of dollars into Bitcoin firms recently.

Corporate funding into Bitcoin & Blockchain infrastructure is growing and generating interest in several segments. Nasdaq is tapping blockchain technology to create a more secure, efficient system to trade stocks.

Conclusion

Blockchain is Bitcoin’s backbone technology. The distributed ledger functionality coupled with the security of Blockchain makes it a very attractive technology to solve the current financial as well as non-financial industry problems.
As far as the technology is concerned, the cryptocurrency-based technology is either in the downward slope of inflated expectations or in trough of disillusionment as shown in Figure 10 in the next page.

There is enormous interest in BlockChain-based business applications and hence numerous start-ups working on them.

The adoption definitely faces strong headwind as described before. However, even large financial institutions such as Visa, Mastercard, Banks, and NASDAQ, are investing in exploring applications of current business models on BlockChain. In fact, some of them are searching for new business models in the world of BlockChain.

Some would like to stay that they are even ahead of the curve in terms of transformed regulatory environments for BlockChain. We envision BlockChain technology going through slow adoption due to the risks associated. Most of the start-ups will fail with few winners. Having said this, we should be seeing significant adoption in a decade or two.

References
Abstract

Meat production will be unsustainable by 2050 at current and projected rates of consumption due to high resource intensity and destructive cost. This opens a large market for nutritious protein alternatives which can provide comparable taste, texture, and nutrition density.

This paper looks at the impacts of industrialized meat production and population demands to estimate the inflection point by which meat-rich diets become unsustainable. We also evaluate the total available market for meat alternatives, current players, barriers to entry, and opportunities for future innovation.
“It turns out that producing half a pound of hamburger for someone’s lunch a patty of meat the size of two decks of cards releases as much greenhouse gas into the atmosphere as driving a 3,000-pound car nearly 10 miles.”

-Scientific American\(^2\)

Impacts of Meat Production

Carbon Footprint

Agriculture is one of the primary drivers of climate change, estimated globally at 14%-15% of all greenhouse gas (GHG) emissions, half of which is generated directly by livestock\(^1\). If we consider both direct and indirect emissions from livestock, many articles cite this as comparable to or exceeding the emissions impact of the global transportation sector.

Livestock produces significant amounts of methane as a natural byproduct of digestion. Referred to as enteric fermentation, this process accounts for 40% of all methane emissions from agriculture\(^1\).

In the ten years between 2001 and 2011 alone, emissions from enteric fermentation increased 11\(^\circ\). Manure management and farming application generate an additional 25.9\(^\circ\)\(^1\). Also notably, 72% of all livestock emissions is generated by cattle\(^1\).

Sources estimate the production of red meat to dwarf all other livestock on environmental impact, with cattle utilizing 28 times more land and 11 times more water than swine or chicken. Compared to staples such as potatoes, wheat, and rice, the impact of beef per calorie is even more extreme, requiring 160 times more land and producing 11 times more greenhouse gases\(^4\).

To generate an emissions measurement based on dietary choice, a 2014 British study on the environmental impact of diet concluded that dietary GHG emissions in self-selected meat-eaters are approximately twice as high as those in vegans\(^5\). The study ran across 2,841 vegans, 15,751 vegetarians, 8,129 fish-eaters and 25,280 meat-eaters and adjusted for gender and age. The findings estimate that meat-rich diets, defined as more than 100g per day, ran the equivalent of 7.2kg of carbon dioxide emissions. In contrast, vegans consumed only 2.9kg of CO2 per day, while meat-free diets produced only 2.9kg.

Thus all studies make the case that significant reductions in meat consumption would lead to significant reductions in GHG emissions. In particular, changes in both livestock management and dietary choice offer strong opportunities. On the supply side, crop management practices such as improved waste and fertilizer management offer the greatest reduction potential at relatively low costs. Better management of grazing land, such as rotating usage, altering forage composition, and restoring degraded lands are also important\(^6\). On the dietary side, shifting away from meat and especially beef consumption offers the greatest potential for reducing emissions.

Health Implications

A 2011 study by the National Antibiotic Resistance Monitoring System, a joint collaboration between the FDA, CDC, and the U.S. Department of Agriculture reports that contaminated meat and poultry infect 3.6 million annually, killing at least 1,000\(^6\).

In the 1920 store-bought meat sampled, antibiotic-resistant strains of salmonella and Campylobacter were found in 81% of ground turkey, 69% of pork chops, 55% of ground beef, and 39% of chicken wings, breasts and thighs. In total, 62% of samples tested positive for antibiotic-resistant strains of Enterococcus, indicative of prior contact with fecal matter\(^7\).

Additionally, there is some evidence that Alzheimer’s and mad cow disease are related. The practice of feeding rendered cattle meat and chicken feces to living cattle opens the doorway to prions which are understood to cause mad cow disease. Eating beef from cattle that have been fed rendered cattle meat transfers these prions into the human bloodstream\(^8\).

Pollution

Pollution from meat production comes from the following sources: Livestock are typically fed corn, soybean meal and other grains which have to first be grown using large amounts of fertilizer, fuel, pesticides, water and land. EWG estimates that growing livestock feed in the U.S. alone requires 167 million pounds of pesticides and 17 billion pounds of nitrogen fertilizer each year across some 149 million acres of cropland. The process generates copious amounts of nitrous oxide, a greenhouse gas 300 times more potent than carbon dioxide, while the output of methane, another potent greenhouse gas, from cattle is estimated to generate some 20 percent of overall U.S. methane emissions\(^11\). Livestock production accounts for 9% of carbon dioxide and 35% of methane gas emissions worldwide.

 Destruction of forests: up to 91% of Amazon destruction is for livestock or livestock feed\(^14\). The trees of the Amazon contain 90–140 billion tons of carbon equivalent to approximately 9–14 decades of current global, annual, human-induced carbon emissions. Beyond its role as a giant, somewhat-leaky reservoir of carbon, the Amazon is home to one out of every five mammal, fish, bird and tree species in the world. Less recognized, perhaps, is the role of the Amazon in the global energy and water balance. Approximately eight trillion tons of water evaporate from Amazon forests each year, with important influences on global atmospheric circulation. The remainder of the rainfall entering this enormous basin flows into the Atlantic Ocean—15–20% of the worldwide continental freshwater runoff to the oceans\(^11\).

Figure 1: Emissions by Sector. Average 1990-2012.

Figure 2: IFAP Source-To-Effect Paradigm

CAFO manure has contaminated drinking water in many rural areas, caused fish kills, and contributed to oxygen-depleted “dead zones” (areas devoid of valuable marine life) in the Gulf of Mexico, the Chesapeake Bay, and elsewhere. Ammonia in manure contributes to air pollution that causes respiratory disease and acid rain. Leakage under liquid manure storage “lagoons” pollutes ground water with harmful nitrogen and pathogens, and some lagoons have even experienced catastrophic failures, sending tens of millions of gallons of untreated waste into streams and estuaries, killing millions of fish\(^14\).

The American Society of Agricultural Engineers provides an estimate of 540 million metric tons of dry weight excreta per annum (American Society of Agricultural Engineers, 2005)\(^12\).

In the US, 89% of antibiotics usage is for animal farming. Between 30 and 90% of the dosage is excreted and flows directly into the environment.

In the US, animal farming is estimated to account for 55% of soil and sediment erosion, 37% of nationwide pesticide usage, 80% of antibiotic usage, and more than 30% of the total nitrogen and phosphorus loading to national drinking water resources.
Figures 2 and 3 are from “Environmental Impact of Industrial Farm Animal Production”, a Report of the Pew Commission on Industrial Farm Animal Production15.

**Ethics**

More than 56 billion farmed animals are slaughtered annually, many of which go through immense pain in the process.

“All dairy cows eventually end up at slaughter. The abuse wreaked upon the bodies of female dairy cows is so intense that the dairy industry also is a huge source of downed cows. Cows referred to as downed cows are so sick and/or injured that they are unable to walk or even stand, hence the title ‘downed’. Downed cows are routinely dragged or pushed with bulldozers in an attempt to move them to slaughter. Dairy cows are not given any food, water, or protection from the elements during their inevitable journey to the slaughterhouse. Prior to being hung up by their back legs and bled to death, dairy cows are supposed to be rendered unconscious, as stipulated by the federal Humane Slaughter Act17. However, this “stunning” which is usually done by a mechanical blow to the head, is terribly imprecise. As a result, conscious cows are often hung upside down, kicking and struggling, while a slaughterhouse worker makes another attempt to render them unconscious. Eventually, the animals’ throats will be sliced, whether or not they are unconscious.”

-MSPCA-Angell

**Questions**

The ethical issues fall into one or more of the following concerns:

Q: Is it ethical to grow and kill sentient beings for our needs especially when alternatives are available?

Q: Even if we grow and kill animals for our needs, is it ethical to subject sentient beings to lifetimes of extreme pain and suffering?

Q: Is it ethical to divert 40%+ of our global agricultural output towards meat production (which only a small percent of the population can benefit from) when close to a billion people still do not get enough to eat?

Q: Is it ethical to destroy so much of the environment to support what amounts to lifestyle choices?

**Government Subsidies**

In most of the countries, the meat industry gets more subsidies from the government than the fruit and vegetable industries though the same governments recommend their citizens to eat more vegetables and fruits.

The U.S. government spends $38 billion each year to subsidize the meat and dairy industries, but only 0.04 percent of that (i.e. $17 million) each year to subsidize fruits and vegetables. A $5 Big Mac would cost $13 if the retail price included hidden expenses that meat producers offload onto society. A pound of hamburger will cost $30 without any government subsidies.

**Inflection Point**

While not too many people are aware of this, the current capacity of the planet cannot support our current or projected rates of demand for food and water. The world’s population is projected to grow from about 7 billion in 2012 to 9.6 billion people in 205019. More than half of this growth will occur in sub-Saharan Africa, a region where one-quarter of the population is currently undernourished.

In addition to population growth, world’s per capita meat and milk consumption is also growing, especially in China and India, and is projected to remain high in the European Union.
A parallel could be drawn to the growth of renewable energy versus fossil fuels. The environmental impacts of carbon-based fuels resulted in policy changes that encouraged investments in renewables resulting in several new markets opening up such as the cars and batteries markets. In 2013, more renewables capacity was added than it had been conventional and renewables well positioned to lead world power growth.

In fact, some food manufacturers petitioned Congress to tackle climate change on Oct 01, 2015. We could see the same market explosion with meat alternatives.

The revenues of meat, beef and poultry processing have steadily increased at a 3% CAGR from 2009 to 2014. This represents a mature market. If we assume a 5% to 10% conversion of this market to meat alternatives we arrive at a market estimate of $10 to $20 billion dollars.

The worldwide meat industry is dominated by just 10 firms with approximately $200 billion dollars in sales annually.

Agriculture currently contributes nearly one quarter of global greenhouse gas emissions, uses 37% of land mass (excluding Antarctica), and accounts for 70% of all freshwater withdrawn from rivers, lakes, and aquifers.

Linearly extrapolating to 2050, these numbers would be 69% of land mass, and 118% of all freshwater! Even with simple math, this is clearly not even feasible.

This picture is further complicated by climate change, which is expected to negatively impact crop yields, particularly in the hungriest parts of the world, such as sub-Saharan Africa.

Growing water use and rising temperatures are expected to further increase water stress in many agricultural areas by 2025.

### Solutions

The biggest intervention people could make towards reducing their carbon footprints would not be to abandon cars, but to eat significantly less red meat.

Beef is the least efficient source of calories and protein, generating six times more greenhouse gas emissions per unit of protein than pork, chicken, and egg production. Shift just 20 percent of the anticipated future global consumption of beef to other meats, fish, or dairy could spare hundreds of millions of hectares of forest and savannah.

Shift to meat alternatives, by producing foods with the protein density of meat directly from plants.

"If all the grain currently fed to livestock in the United States were consumed directly by people, the number of people who could be fed would be nearly 800 million," reports ecologist David Pimentel of Cornell University's College of Agriculture and Life Sciences.

### Estimated Market Size for Meat Alternatives

This report estimates the market for meat alternatives to be between $5 and $10 billion dollars. A couple of different approaches were taken to estimate the market for meat alternatives:

1. Conversion of existing market for meat products to plant based products
2. Projecting growth of existing market for meat alternatives

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The worldwide meat industry is dominated by just 10 firms with approximately $200 billion dollars in sales annually.
Given the high levels of government subsidy (e.g. US $22 billion in the United States, and $33 billion dollars in other OECD countries) the industry is susceptible to disruption by both policy changes and individual choice. Furthermore, climate-driven disruptions such as feed supply could lead to a shock that could drive the market for alternatives further.

Factors in Market Conversion

People looking to eat less meat for health reasons, including weight, diabetes and heart disease management. Cost of meat production increasing driving less demand. More awareness of environmental impacts of meat production and processing. More affluent in regions of the world which are already primarily vegetarian such as India will lead to these demographics looking for high quality plant-based protein.

Sports nutrition, driven by explosion in protein bars sales and offerings. Ethical concerns driving people to re-examine the impacts of their dietary choices.

Existing Market for Meat Alternatives

The existing global meat alternative market is expected to reach USD 5.17 billion dollars by 2020 at a CAGR of 6.4% from 2015 to 2020. The market has been segmented on the basis of type into:

1. Tofu & tofu ingredients
2. Tempeh
3. TVP (a highly nutritious and versatile soy product, that takes on flavor easily)
4. Seitan (derived from the protein portion of wheat. It stands in for meat in many recipes)
5. Quorn (a fungus-based ferment used in food production as a meat substitute.)
6. Other soy-products (miso, yaso, & natto)
7. Others (lupin, pea-protein, risou, and valess)

The soy-based segment accounted for an approximate 68% market share in the global meat substitutes market in 2014. The market for tofu and tofu ingredients is projected to witness the highest growth as a result of increasing awareness about the health benefits of soybean.

Leading players in the meat substitutes market include:
1. Amy’s Kitchen (U.S.)
2. Beyond Meat (U.S.)

Meat Alternatives

Soy Alternatives

Value Proposition

Soy meat alternatives are generally composed of soy protein, wheat gluten, spices, dairy, and carbs. Soy is well regarded as a high-quality protein containing all essential amino acids needed for growth, B vitamins, iron, fatty acids, dietary fiber, omega 3s, and isoflavones. Additionally, soy is naturally cholesterol-free and low in saturated fat. Studies also show that choosing soy-based foods over animal fats may help lower LDL, or “bad” cholesterol, by 3%.

The more common forms of soy alternatives today are tempeh and textured soy protein. A staple of Indonesia, tempeh is a cake of cooked, fermented soybeans. It is optionally combined with legumes, grains, and seeds and is made by fermenting dehulled soybeans for 18-24 hours with a starter till a white mold binds the ingredients together. Good tempeh yields a firm, chewy texture with a mushroom or yeast flavor.

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Future Innovation

Soy itself has been a standalone staple of its own across cultures for generations, with a wide range of applications. The soy-based meat alternatives market is projected to reach $5.17 billion dollars by 2020.

Plant-Based Alternatives

Value Proposition

One of the biggest challenges in reducing the consumption of animal protein is that humans like the taste and texture of meat. Meat is an important part of the human culture across the world. In order to address this, several companies are working on products that mimic the taste, texture and nutrition profile of meat. These products are either proteins derived from plants or with the taste...
textured and nutritious profile of meat, or they may be actual animal meat that is directly cultured in the lab. In this section, we will look at the companies that are producing products from plants that mimic the taste, texture and nutrition profile of meat.

**Lab Grown Meat**

**Value Proposition**

The lab-grown meat, also known as cultured meat or vitro meat is produced by taking a small amount of cells from a living animal and growing it into lumps of muscle or whole pieces of meat that wouldn’t be made of fetal bovine serum (from unborn cows). He is also working on the fat tissue which is important for the iron content and the red color of beef. And last but not least, Post is trying to scale up production by developing special tanks for growing the cells.

Creating cultured steaks, chops and other whole pieces of meat is a possibility for the distant future, and other whole pieces of meat is a possibility for the distant future, but Post believes that in 5 to 7 years consumers will be able to find cultured ground meat products on the shelves of high-end stores in the United States. Such meats could be produced locally or in places like Dubai or Silicon Valley and would cost around $30 to $45 per pound, says Post, and should taste the same as the real thing. Finally, with lab grown meat, one can get actual meat without it having come from animals.

**Taste and Texture**

It can be difficult to replace the taste and texture of meat. This in turn can make it harder for current meat eaters to switch to alternatively derived meat.

**Beyond Meat**

- **Founded**: 2009
- **Funding**: $17M funding in 2 rounds
- **Availability**: Products found in 7,300 stores, and will soon be in Walmart as well. Aiming to get its products on pizzas and in fast-food restaurants and to targeting the average consumer.
- **Other Information**: Interview by The Atlantic, Technology leaders have been fooled (Bill Gates blog)

**Impossible Foods**

- **Founded**: 2011
- **Funding**: $183M in 2 rounds from 5 Investors
- **Availability**: 2016
- **Other Information**: New generation of meats & cheeses from plants, Mission: to give people great taste and nutrition minus negative health & environmental impact.

**Hampton Creek Foods**

- **Founded**: December 01, 2011
- **Funding**: $120M in 5 rounds from 24 Investors
- **Availability**: Multiple locations
- **Other Information**: Egg and Mayo replacements, One time target of disinformation campaign by Egg Board

**Political Roadblocks**

The meat industry is a very powerful political lobby and will do everything it can to prevent the rise of alternatives that could affect its economics. It has worked successfully to both lobby and financially support members of congress and the USDA to prevent changes to the food production facilities are inspected, as well as fighting changes to the food pyramid that could reduce the recommended daily allowances of meat.

**Possible FDA Regulations**

While there has not been any requirement to have the meat alternatives certified by the FDA, this may become an issue. The latter could be because of the following reasons:

1. The meat alternative production process may trigger a review by the FDA
2. The unexpected appearance of health-related issues caused by any specific meat alternative

However, it is not likely that the former could constitute major barriers for the adoption of meat alternatives.

**Barriers To Entry**

**Culture**

This is perhaps the most difficult to overcome. Meat has great cultural significance, not the least being that it is an aspirational food. When one comes out of poverty, one expects to eat more meat. Furthermore, not eating meat is considered to signify a loss of prestige or economic standing. Eating meat is also considered macho, and eating less of it is considered a sign of weakness.

However, just as the use of clean energy vehicles underwent a cultural transition (and is now considered a status symbol, like in the case of Tesla), attitudes towards meat eating can change.
It is clear that meat production is unsustainable at current and projected rates of consumption due to its extremely high resource intensity and destructive cost. Researchers are clear that one of the most effective ways to reduce the harmful effects of meat production is to eat less meat.

We believe that this opens a huge ($5B-$10B) market for nutritious protein alternatives which can provide comparable taste, texture, and nutrition density as animal meat. We have seen this thesis proven over the past 5 years, supported by the increased number of companies working on and producing meat alternatives, as well as via research in top universities and large investments from the venture capital community.

Much like the growth of the renewable energy market, we expect that there will soon be a tipping point when the quantity of environmentally friendly, cruelty-free alternatives will surpass and overtake the production of animal meat.

The time to invest in meat alternatives is now. Now is a great time for both the portfolio and the planet.

References
Abstract

The adoption of 3D printing, also commonly referred to as additive manufacturing, is occurring at a very rapid pace with a further projected growth of 45% compounded annual growth rate (CAGR) over the coming years. An important aspect of the widespread acceptance of industrial 3D printing has been an industry-wide focus on improving quality, reliability and repeatability of 3D printed parts. Industry stakeholders, including printer manufacturers and industrial end users of parts, have identified further quality assurance through internationally established standards, verification, and certification as essential to spur even more rapid technology adoption and implementation.

In this paper we begin by presenting the basics of 3D printing technology and then turn to explore the unique challenges that 3D printing poses with respect to ensuring the production of high quality parts. Additionally, we present an overview of the current stakeholders for 3D printed parts’ quality standards and verification mechanisms. Lastly, we examine the current trends to lower costs for quality assurance of the burgeoning 3D printed parts market, which include systemic aggregation of quality assurance programs and new low cost measurement technologies.
Introduction: 3-D Printing Verification

Twenty years ago, 3D printing, also commonly referred to as additive manufacturing, was perceived as a futuristic technology; a novelty whose promise was decades away and though intriguing left too many gaps with respect to conventional manufacturing to be considered for widespread use. In the decades since, through refinement of techniques and the identification of new technologies, 3D printing has advanced significantly to the point that the incorporation of 3D-printed parts in high-end industrial components is rapidly becoming commonplace.

Industrial adoption of 3D-printed parts is occurring at a very rapid pace with a further projected growth of 45% compounded annual growth rate (CAGR) over the coming years. An important aspect of this widespread acceptance has been an industry-wide focus on improving such parts’ quality, reliability, and repeatability. Industry stakeholders, including printer manufacturers and industrial end users of parts, have identified further quality assurance through internationally established standards, verification, and certification as essential to spur even more rapid technology adoption and implementation.

Quality assurance companies have created departments focused specifically on the 3D printing market. Moreover, several national and international consortia and government agencies have embarked on multi-year programs to define worldwide standards to ensure the quality of 3D printed parts. At the culmination of these programs, the consortium expects to make a worldwide presentation of detailed standards regarding the qualification and processing of materials, as well as new testing guidelines.

But the path to the full implementation of such standards is not a clear one. Based on the potential explosion in scale of new printing devices, printable materials, and printing applications, we anticipate a gap in the capability of the industry to enforce the new standards and continue to develop additional characterization methods in order to keep pace. With respect to the sheer size of the new market, we project that quality assurance aggregators will streamline testing and certification costs in the 3D printing industry as they have demonstrated in the conventional manufacturing space.

With respect to new materials and characterization technologies, we predict that new technical solutions such as low cost dimensional measurement will be developed and proliferate through the marketplace.

1. The State of 3D Printing Technology

Thousands of 3D printers are available in the market today, and just about every other week a new model of 3D printer is introduced. The price of these printers ranges from a few hundred dollars at the entry level, to the level of “sky is the limit” (high-end, special size/materials).

Printers, manufacturers, software developers, service providers, and 3D printing users are rushing to the marketplace with new business models created daily. Some of the most important developments are highlighted in the following sections.

1.1. Materials and Printer Types

A wide range of materials is available for 3D printing. The most commonly used materials are the following:

- Polylactic Acid (PLA): Easy for printing, plant-derived and biodegradable, available for various color and rigidity levels.
- Nylon: Slippery and slightly pliable. Good for parts requiring low friction. Some take on dyes well, and can be particularly strong.
- Stainless Steel: Typically infused with bronze. Cheapest form of metal printing. Very strong and suitable for significantly large objects.
- Titanium Alloys: Powders are sintered together by laser to produce metal parts.
- Polycarbonate (PC): 3D printers use plastic filament. The most popular—and cheapest—3D printers use plastic filament. If 3D printing becomes industrialized, disposal of this byproduct will become a new environmental issue.
- Polyjet: Works by jetting photopolymer materials in ultra-thin layers (16µm) onto a build tray until the part is completed. Each photopolymer layer is cured by UV light immediately after it is jetted.
- Stereolithography (SLA): Method based on the hardening of successive layers of fluid resin using UV rays or lasers. After each layer is fused, the perforated platform is lowered very slightly and another slice is traced out and hardened by the UV laser. This process is repeated until a complete object has been printed.

1.2. Challenges with 3D printing materials

Despite the rapid advancement, 3D printing materials still face the following challenges:

- Strength: 3D printed parts are not as strong as traditionally manufactured parts. Their layer-by-layer technique of manufacturing is both their biggest strength and their greatest weakness. Metal printing very often uses powder metals, which contain oxides, which not only make the metal rust more easily, but also act like holes in Swiss cheese which weaken the final products.
- Energy inefficiency: According to research done by Loughborough University, melting or fusing 3D printing materials consumes about 20 to 100 times more electrical energy than injection molding, casting or machining in order to make an item of the same weight.
- Reliance on plastics: Environmental movements in recent history have attempted to reduce reliance on plastics, from grocery bags to water bottles, and replace them with ones that can be made from recycled materials. The most popular—and cheapest—3D printers use plastic filament. If 3D printing becomes industrialized, disposal of this byproduct will become a new environmental issue.
- Safety concerns: 3D printer poses a serious health risk when used inside the home. The printers emit particles in great numbers and can cause serious health-related issues.

In particular, there are additional challenges for 3D printing metal materials. A clear example of this is the higher temperature level required to print metal objects, which in turn translates to even higher energy consumption and a higher manufacturing cost for 3D printed products.
2. 3D Printing Business Models

2.1 Major market trends

Industry analysts predict tremendous growth opportunities in the 3D printing business for the next few years. The trend is consistent across all 3D printing segments and regions, as indicated by Figure 1 and Figure 2.

2.2 Industrial 3-D Printing

Industrial 3-D printers generally have larger print throughput capacities, top-notch resolution and use significantly durable printing materials.

2.2.1 Major companies moving into industrial 3-D Printing

Up to now, 3-D printing has been most useful in creating prototypes. But from the automotive to the electronics and toy industries, 3D printers will increasingly produce critical parts and finished products. For example, Bentley is one company that has already demonstrated the feasibility of using 3D printing for small, complex parts. Motorcyclists and bikers will also be able to order their own customized helmets that are printed to fit their individual head size and structure.

2.2.2 Why companies will choose industrial 3-D Printing

Industrial 3-D printers are superior to consumer-grade 3D printers for manufacturing fully-functioning, quality prototypes. As mentioned before, the best industrial 3D printers have large print capacities, top-notch resolution and use extremely durable materials. These printers make manufacturing a much simpler process for individual users and companies.

Figure 2: The Current Bouquet of 3-D Printing Materials Market

2.3 3-D Printers for small business and Home Use

Providers of such services include: Shapeways, LMaterialise, Ponoko, RedEye, Sculpteo. The advantages and disadvantages for 3-D printing outsourcing to an external provider are the following:

Advantages
- Cost of owning 3D printers
- Design services for customers without CAD experience
- Quality: Special printer capabilities
- Volume: Larger quantities
- Materials: Special materials

Disadvantages
- Iterations can be slow and expensive

II. Methods of 3D printing standards and verification

All the major stakeholders in 3D printing commerce recognize the need for well-defined standards, verification and certification mechanisms. Printer and material manufacturers seek to differentiate their products based on their ability to print high-quality parts. These manufacturers research and report on the capabilities of their printers and materials. However, the definition of “high quality” must be universally defined and accepted by the industry. National and international quality consortia and government agencies have traditionally held the role of defining objective, repeatable, and enforceable standards in the manufacturing industry as a whole. These consortia are, generally speaking, public-private organizations that convene to define common standards for materials, materials testing, and dimensional analysis.

1. Role of consortia

1.1 Major Consortia Players

The types of consortia and government agencies associated with 3D printing standards and verification can be loosely grouped into two categories. Firstly, there is a traditional manufacturing standard-and-testing consortia as well as government agencies that have created subgroups to specifically address the unique challenges of 3D printing. Secondly, there are 3D printing industry and printing users consortia.

The foremost of the traditional manufacturing standards consortia to establish standards in additive manufacturing is the American Society of Testing and Materials (ASTM) which formed a technical committee (ASTM F42) for additive manufacturing in 2009. ASTM F42 convenes bi-annually with participation of approximately 70 of its 215 members. The organization lists its scope as “The promotion of knowledge, stimulation of research and implementation of technology through the development of standards for additive manufacturing technologies.” Moreover, it states that the work of the organization will be coordinated with other ASTM technical committees and other national and international organizations having mutual or related interests.

ASTM’s international counterpart, the International Organization for Standards (ISO) also established a technical committee (TC261) for additive manufacturing in 2011. Nineteen participating countries are currently listed as ISO TC 261 members. The scope of the technical committee is defined as “Standardization in the field of Additive Manufacturing (AM) concerning their processes, terms and definitions, process chain (Hard- and Software), test procedures, quality parameters, supply agreements and all kind of fundamentals.” In November of 2013, ISO and ASTM published a joint plan to unify ASTM and ISO additive manufacturing standards. ASTM’s analysis of the structure of required standards is presented in Figure 3.

Consortia specializing in the development of the 3D printing industry as a whole as well as those including 3D printing as a primary focus include the Additive Manufacturing Users’ Group (AMUG), America Makes (The National Additive Manufacturing Innovation Institute), and the Additive Manufacturing Consortium (AMC), and a European consortium, the Support Action for Standardization in Additive Manufacturing (SASAM).

1.2 Details of when Agencies will Release Standards

Two U.S. governmental organizations worth noting for establishing 3D printing verification standards were the National Institute of Standards and Technology (NIST) and the National Additive Manufacturing Innovation Institute (NAMII). NIST released their initial standards project in 2010 and followed up with a 3D printing measure in 2014. The National ADDitive Manufacturing Innovation Institute (NAMII) also released their initial standards measure in 2015. Other major consortia with committees and activities related to additive manufacturing include the American Society of Mechanical Engineers (ASME), the Society of Manufacturing Engineers (SME), the Society of Automotive Engineers (SAE), and the American Society of Precision Engineering (ASPE).

Figure 3: Structure of AM Standards
and techniques include the National Institute of Standards and Testing (NIST), and Oak Ridge National Laboratory (ORNL). A sample test artifact is shown in Figure 4. NIST’s Measurement Science Roadmap is presented in Figure 5.

The ORNL contribution to additive manufacturing as a whole is broader in scope than that of NIST. ORNL has partnered with America Makes and AM to host additive manufacturing conferences and has also participated in projects to demonstrate advanced 3D printing techniques, such as printing a Shelby Cobra for the Detroit Auto Show in January of 2015. With respect to additive manufacturing verification, ORNL has a specialized metrology initiative using neutron characterization techniques to measure geometric tolerances and map residual stress in 3D printed components.

1.3 Role of Non-profits and Universities

Several universities have research programs in additive manufacturing which include elements of 3D printing verification. Some notable examples include an America Makes sponsored project involving North Carolina State University, Iowa State University and several corporate sponsors “to create a system that will be able to produce a mechanical product to final geometric specification”. Another university based effort is the Rapid Prototype Consortium (RPC) of the Milwaukee School of Engineering (MSOE). The MSOE also partners with America Makes and SME to offer a certificate in Additive Manufacturing through which practitioners can become certified by passing an exam on the collective “body of knowledge” of additive manufacturing.

There are also other emerging programs in 3D printing user certification; for example, NYU’s School of Professional Studies offers certificate programs in 3D Modeling and Printing, as well as 3D Design and Fabrication.

2. Role of Manufacturers in standards and verification

2.1 Manufacturers Internal Quality Assurance

While 3D printer manufacturers and service providers are certainly highly active participants in the previously mentioned consortia, they also seek to define and differentiate their product offerings based on their ability to print high quality parts on a more fundamental level. For example, Stratasys, a leader in Fused Deposition Modeling (FDM) of thermoplastics, has published a white paper available for download on their website entitled “The Accuracy Myth” authored by Bonnie Meyer (Figure 6), addressing a quality emphasis on dimensional accuracy and repeatability. The purpose of the white paper is to establish the long term dimensional stability of FDM printed parts manufactured on a Stratasys printer while assuring the end user of the capability of Stratasys materials and printers.

2.2 Manufacturers Partnerships

Major 3D printer manufacturers have also embarked on partnerships with their industrial customers. One notable example is the partnership between EOS GmbH, the industry leader in printer manufacturing for laser sintering of metal alloys, and MTU Aero Engines, a German aerospace engine manufacturer. In January of 2015, EOS and MTU announced their plans to integrate an MTU-developed metrology technology described as “Optical Tomography” on EOS systems to monitor laser energy and material sintering properties in real time to help ensure material quality and integrity.

3. Ranking and Crowd-sourced Quality

At the lower end of the 3D printing quality and service spectrum are efforts of printing services to crowd-source quality control through user assessment and feedback. An example of this method is the design ranking feature of the Shapeways 3D printing service. Regulation of quality with respect to design integrity is done by labeling product designs as “Never Printed Before”, “First to Try””, “Below 50% - Not Printable”, “50-80% - First to Try”, and “80% and above”. One may make note of the fact that a design can be rated as “Product” quality despite the one in five chance that it might not print.

3.1 User-Generated Quality Standards

Another example of crowd-sourced quality includes a user-generated database in the “3D Printing Tests” section on MarkerBot’s Thingiverse website. Through this database, users generate and share their own quality test structures and describe in detail the parameters employed to print the object. In the representative sample in Figure 6 the user dated a test printing file and a picture of the final result as well as detailed instructions regarding the machine printing speed used. The purpose of this test fixture is to demonstrate the finish and resolution of the MakerBot Ultimaker 2 as a function of printing speed and temperature.

III. Market Opportunities

1. Established Quality Companies

Currently there are companies and non-profit organizations which offer standard compliance auditing and

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Figure 4: NIST Test Artifact

Figure 5: NIST Measurement Science Roadmap Manufacturing Report

Figure 6: “The Accuracy Myth” by Bonnie Meyer
safety certification, and coordinate standards across multiple OEMs. Such companies include the Underwriter’s Laboratory (UL), Sigma Labs, Intertek, American Association for Laboratory Accreditation (A2AL), and the Performance Review Institute (PRI).

For example, UL provides product review, compliance services and certification in the additive manufacturing (3D printing) space. This services include addressing equipment and materials compliance, as well as providing printed parts and product validation for the medical, automotive, building materials, jewelry, household products, and electronics industries.

An emerging trend is the consolidation of partnerships at the high-end 3D printing space, where there is a price premium and requirement for quality, which ultimately validates the need for the services outlined above. For example, GE awarded $500,000 to Sigma Labs, which announced the PrintRite3D software. Effective software algorithms reduce 3D printing time and waste, such as comparison of 3D geometric data and validation of translated models. The typical considerations include: (a) correctly define printer boundary conditions and nozzle diameter of the 3D printer, (b) manually define additional needed features, such as support structures to properly construct the printed parts, (c) define the position of normal vectors of the meshes in the .stl file, and (d) ensure that the 3D surface should be closed. In addition, the software algorithm should be able to highlight the problem area for the users and suggest corrective action.

For users who don’t want to use professional 3D software, .stl files can be downloaded from a 3D database, such as Thingiverse, GrabCAD, Ponoko or Nervous System. Those designs can then be customized using a WebGL-based 3D modeling tool. For in-browser 3D modeling environments, controllers such as “Leonardo” by Leoply can help the user navigate and work in a 3D virtual reality space.

When the 3D model is finished, it can be verified before printing using Netfabb for mesh repair function, Willis3DPrint, or Blender. After verification, the model is sliced to generate a G-code which defines the tool path for the extruder head of the 3D printer firmware. Codes for the 3D printer head movements follow a NIST G-code standard.

Another example is EOS partners, partnering with MTU, whose Optical Tomography (OT) augments the monitoring capabilities by using multiple sensors to verify system status, and camera based OT technology to control the exposure processes. Those in turn ensure the material quality and finish.

1.2 Role of Quality aggregators - web based market efficiencies

Outside the high-end 3D printing market where quality standards must be met, another emerging trend is the emergence of web based aggregators which reduce qualification costs while maintaining quality standards. Such aggregators include the Interlink program by Intertek, Net-inspect, and PRI’s Nadcap and MedAccred programs. These service providers act as clearinghouses to link certified parts manufacturers to commercial/end customers. This type of service could easily extend to encompass 3D printed parts. For example, MedAccred, destined for medical application parts, could include a 3-D printed knee replacement component.

2. Emerging Tech opportunities

2.1 3-D Scanning and Imaging

3D scanners analyze a real-world object to collect data and then construct 3D models, using optical technologies, tomography scanning, contact mode or non-contact mode scanning. A coordinate measuring machine (CMM) is an example of a high precision contact mode scanner, frequently used in manufacturing. Non-contact active scanners emit radiation or light, ultrasound, or X-rays. For example, a 3D laser scanner is an active scanner using laser light to probe the subject using the time-of-flight laser range. A triangulation-based 3D scanner laser for 3D modeling processors, which can lead to enhanced or reduced reliability of the parts or products. The reliability SPEC is based on specific applications. Since the process flow is different from “subtractive manufacturing”, the requirement of specification needs to be studied in detail when those 3D printed parts are used for critical applications, such as high performance mechanical applications or medical devices.

Additional 3D scanning techniques include computed tomography (CT), which generates a large series of 2D X-ray images. It produces a discrete 3D volumetric representation and corresponding 3D surface.

2.2 Lower cost coordinate measurements

Low cost digital metrology is becoming available which will enable a wider usage of 3D printing. Examples include the iSense 3D Scanner for Apple’s iPad and Mac products, RealSense 3D Camera for Intel’s tablets/phones, and HP Sprout computers.

The iSense 3D scanner is integrated with companies such as Cubify.com to accompany their 3D printers. Those 3D scans can be uploaded directly for 3D printing either at home or through cloud printing. Intel’s RealSense is an integrated 3D camera which tracks points of a moving object to form 3D images. The scan can then be saved and shared digitally, or printed with the use of 3D printer. HP’s Sprout Computer uses DLP Projector technology and Intel’s RealSense 3D camera to capture a 2D or 3D object.

2.3 Lower cost materials characterization

The steps of the 3D printing process involve thermal treatment in order to connect extruded printing materials between and within layers. Such thermal treatment modifies the material properties, which can lead to enhanced or reduced reliability of the parts or products. The reliability SPEC is based on specific applications. Since the process flow is different from “subtractive manufacturing”, the requirement of specification needs to be studied in detail when those 3D printed parts are used for critical applications, such as high performance mechanical applications or medical devices.

For example, when a printed part is used in a highly mechanically stressful application, the tensile and fatigue behaviors must be studied. Often parts for those applications are made of alloys, whose material phases can easily be modified during thermal processes, and need to be analyzed using X-ray diffraction or Cross-section electron microscopes to control and ensure the end-product reliability.

Those material analysis instruments are expensive and not available to most of the machine part manufacturers. Thus, as commercial applications continue to grow, we envision an increasing need of such high-end qualification services. This can lead to additional aggregation to reduce the characterazation cost, and opens the possibility for the generation of new business models and partnerships.

2.4 Self-verification and reporting service

Web-based 3D printing services, such as “crowdsourced reviews and ranking”, provide useful resources for user communities regarding the designs, printers, and material selection, as well as information about rankings designers and companies providing general 3D printing services.

For example, Shapeways is an internet-based marketplace of 3D printing services and reviews (http://www.shapeways.com). Other similar web based marketplace and review forums include Ponoko (http://www.ponoko.com), Sculpteo (http://www.sculpteo.com/en/), and iMaterialise (http://imaterialise.com).

Additionally, for the medium to low-end 3D printing applications where quantitative validation and certification are not required, those “crowdsourced reviews and ranking” websites are effective alternatives for product validation.

Conclusion

The 3D printing market is rapidly expanding and gaining widespread acceptance for industrial applications. Ensuring the manufacturing of high quality, highly repeatable parts through standards and verification is an essential element for speeding the further adoption
of the new technology. Multiple stakeholders are currently addressing the needs for quality assurance with expected completion of the most detailed and stringent international quality standards due in 2018. In the meantime, new technologies may emerge that will require further characterization. Also, due to the high cost of existing characterization techniques and the potential scale of the new market, improvements are needed to reduce the cost of quality assurance programs as well as create new lower cost characterization methods.

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Abstract

Palisade Therapeutics is a new venture with a novel therapeutic approach for treating progressive neurological diseases, with a focus on post-traumatic epilepsy and age-related dementia, two unmet clinical markets with a value estimated at $30 billion. Current drugs suffer from two major shortcomings: they are not personalized and they are not disease-modifying; in other words, they manage symptoms without understanding or treating the underlying causes of neurodegeneration.

We discovered a previously unknown but widespread cause of neuropathology, involving decline in the health of the vasculature resulting in blood-brain barrier (BBB) failure after injury and during aging, which allows molecules to leak from the blood into the brain. One key molecule, albumin, triggers an injury response by activating the transforming growth factor beta (TGF) signaling pathway, leading to neurodegeneration, cognitive impairment, and epilepsy. We treat this target with a two-fold, personalized, disease-modifying approach: 1) Using companion MRI diagnostics to screen patients for vascular permeability; 2) Using IPW, a small molecule TGF receptor (TGFER1) kinase inhibitor, to slow the symptoms and progression of disease in the target population. Our rodent studies show that treatment prevents epilepsy following vascular damage in mice, and improves in cog

itive function after 7 days of IPW treatment in naturally aged, 24 month old mice, while our translational human studies show the presence of albumin and TGF signaling in postmortem tissue, and vascular permeability in MRI imaging of at-risk patients. Beyond age-related dementia, many other diseases have early vascular damage and similar patient outcomes, including stroke, head injury, surgical patients, and others, demonstrating the long-term value of this platform as a new strategy for treating neurological disease.

The Problem

The strategy for treating disease has not changed markedly since the rise of modern pharmaceuticals in the past 50-100 years. The vast majority of drugs do not modify the progression of the underlying pathology. They treat symptoms but they do not cure, and so they must be taken chronically. As they are merely suppressing symptoms, they may be only partially effective and can also carry strong side effects, leaving the patient in a limbo state: not quite sick, not quite healthy, constantly medicated to stave off a decline into full-blown illness. The costs of chronic treatment, to the patient and to our medical system, are enormous.

Consider, for example, the two diseases that we are targeting in our novel therapeutic approach: age-related dementia and post-traumatic epilepsy (PTE). For both, there is currently no diagnostic method to predict who will acquire the disease. We know that certain populations are at risk, but we have no certainty in predicting who will get the disease and who will not. There is no recourse but to wait until end-stage symptoms appear, when it is too late to treat or reverse. Simply put, no one has been able to offer effective preventative or disease-modifying treatments.

In contrast to slow changes in clinical approaches, fundamental biological research has advanced at a startling pace. Compared to 50 years ago, we can now peer into the detailed molecular mechanisms that cause disease, and in doing so understand that many diseases do not appear at random, but rather are triggered by previous life events which set in motion biological changes that only later manifest as pathology. For example, for the past 10 years we have been studying a variety of different diseases that cause acute damage to the brain, such as traumatic injury (TBI), stroke, and brain tumors. While each of these diseases are quite different in the immediate treatment, the long-term outcomes for patients are remarkably similar: regardless of the type of brain injury, patients show a non-specific set of later pathology, ranging from mild cognitive decline and neurodegeneration to, in the most severe cases, appearance of chronic epilepsy14. These pathological endpoints appear after the patient has fully recovered from the initial injury, weeks to months or even years later15,16.

Patient outcomes in traumatic brain injury (for example after a car accident) illustrate this point effectively. Each year there are approximately 2 million cases of traumatic head injury, and 10-40% of these patients later go on to develop epilepsy, while an even larger number show cognitive impairment15,16. Yet despite the clear link between head injury and epilepsy, there is no therapeutic approach to predict or prevent post-traumatic disease; no diagnostics to predict which post-injury patients are at risk, no drugs to prevent disease progression. Rather, post-traumatic epilepsy patients are only diagnosed once chronic seizures appear, and then are placed on anti-epileptic drugs which often fail to control seizures and impose strong cognitive side effects17.

At Palisade Therapeutics, our approach to this problem is completely different. Through sustained research, we have identified the common biological mechanisms that cause the brain to become organized and pathological after injury. By understanding these earliest stages of disease progression, we developed new therapeutics to target the pathways that induce pathology, thereby preventing post-injury changes. In other words, our approach is to prevent brain pathology before it starts, rather than chronically treating symptoms after disease has already progressed to a late, irreparable stage (Figure 1).

Figure 1: Traditional Treatments Focus on Symptoms After They Manifest

<table>
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<tr>
<th>Traditional treatments focus on symptoms after they manifest</th>
<th>Our strategy focuses on early stages of cause disease</th>
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<tbody>
<tr>
<td>Injury and BBB breakdown</td>
<td>Cognitive impairment and epilepsy</td>
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<tr>
<td>Recovery</td>
<td>Latent period (indolent pathogenesis, inflammation surging, neurodegeneration)</td>
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<tr>
<td>Symptoms reported (cognitive impairment, dementia, seizures)</td>
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Figure 1: We identified a common pathological pathway shared across a variety of brain insults; these injuries cause disruption of the blood-brain barrier, inducing an injury response that reorganizes the brain resulting in neurodegeneration, cognitive dysfunction, and epilepsy. As patients experience these injuries, they cause a delayed appearance of subsequent illness that is only treated once endpoint symptoms appear. Our strategy is to treat the root cause of disease, thus preventing the pathology before it starts.
This albumin-induced inflammatory signaling in turn causes a range of pathological outcomes: neurodegeneration and cognitive dysfunction, including neural cell death, reduction in cortical volume, and decrease in brain function, and increases in neural excitability (reduced potassium buffering and changes in proteins regulating excitatory neurotransmitter release) and excitatory connectivity (increased synaptogenesis).

In the most severe cases, a subset of these animals developed chronic epilepsy, mirroring the human clinical condition of PTE. Importantly, because this was a novel role for albumin in causing pathological activation of TGFβ signaling, we also characterized the specificity of this mechanism. We showed that albumin directly binds the TGFβR, and that blocking this binding prevents albumin uptake into astrocytes and initiation of pathological signaling.

Secondly, we isolated the key molecule from the blood that induces the changes, and characterized the molecular mechanisms causing disease.

We found that albumin, the most abundant protein in the blood, activates an inflammatory signaling response when it enters the brain (after BBB disruption). This occurs as a generalized injury response: once BBB is compromised, albumin leaks into the brain and binds to the transforming growth factor beta receptor (TGF-βR), activating this master signaling cascade that regulates inflammation and injury response (Figure 2).

The TGFβR is specifically activated on astrocytes, a type of cell in the brain that serves as an overall sensor and regulator of the brain environment. In turn, astrocytes become reactive, and secrete a variety of molecules via the TGFβ pathway that cause pathological reorganization of the brain and changes in neural function.

In our first phase of research, we showed that BBB disruption is the key cause of pathological changes resulting from head injury, and described the mechanisms that induce pathology. Firstly, we showed that experimentally disrupting the BBB in rodents, without causing any other injury, leads to the major type of brain insult, which in turn allows components of the blood to leak into the brain and perturb its normal functions.

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Because disruption of BBB is so widespread across many different neurological insults, our findings open up the potential for a completely new, preventative therapeutic approach with broad application across different diseases. Initially, we are focusing on targeted entry into two markets that have high incidence and are lacking effective treatments: post-traumatic epilepsy and age-related dementia.

Our Markets

Post-traumatic Epilepsy: Preventing pathology and chronic epilepsy after head injury

Our data shows that blocking albumin induction of the TGFβ pathway can prevent the pathological signaling changes leading to neural hyperexcitability and epilepsy after head injury. To demonstrate the proof-of-principle of this strategy, we tested our therapeutics in three different models of brain injury in rodents, and followed the outcomes with long-term continuous electrocorticographic recordings (ECoG) of brain activity to detect epileptogenesis and seizures in real time. Firstly, we infused albumin directly into the brain via intracerebroventricular (ICV) osmotic pumps, while also co-delivering a TGFβ inhibitor (SN) directly into the ventricles. This shows the fundamental, disease-causing effects that albumin has on the brain, without any other injury, and the effectiveness of blocking the target pathway. Secondly, we opened a surgical window to the cortical surface and perfused albumin onto the surface of the brain, and co-treated with losartan during the surgery. This mimics a superficial injury, such as occurs in head trauma. Finally, we tested a model designed to recirculate the sequence of events that would happen with an actual clinical patient. Rather than surgically administering albumin, we opened the BBB to closely mimic the pathology that occurs in head injury; we then acutely treated with oral administration of losartan for three weeks via the drinking water, as would occur in a theoretical patient taking our preventative therapeutics in the acute phase after injury, during recovery. After the acute administration was halted, and the long-term outcomes were followed. In each of these injury models, most of the subjects developed epilepsy after injury if they were not treated with our therapeutics; in contrast, preventative intervention with our therapeutics completely prevented the onset of epileptogenesis and the appearance of chronic seizures.

Market analysis: Innovation and new treatment approaches in PTE are desperately needed. Epilepsy affects 2.3 million people in the US, with an estimated annual cost of $15.5 billion in healthcare. The market for pharmaceutical treatment of epilepsy generated $12 billion in 2008, and is estimated to increase by 30% by 2016. In cases where the etiology is known, the largest cause of symptomatic epilepsy is trauma (unpublished). We also searched for early signs of neural dysfunction by performing continuous telemetric ECoG recordings from the brains of aging mice, and found the same evidence of albumin and activation of inflammatory TGFβ signaling (unpublished). We further found that the pathological activation of TGFβ signaling in these aged mice was nearly identical to the pathology that we see in young mice with all the hallmarks astrocytic activation and inflammatory signaling that trigger subsequent disease (unpublished). Critically, we found that treating mice with a daily dose of IPW can reverse reactive glial and inflammatory signaling. Similarly, we obtained post-mortem sections from aged human brains, and found the same evidence of albumin and activation of inflammatory TGFβ signaling (unpublished). We also searched for early signs of neural dysfunction by performing continuous telemetric ECoG recordings from the brains of aging mice, and found that aging mice show slow wave activity typical of smooth wave rhythms during normal brain function, which are absent in young mice; the same shifts in slow wave power in brain activity were seen in young mice when after treatment with albumin to induce inflammatory signaling (unpublished). Together, these data suggest that BBB breakdown and inflammatory TGFβ signaling may be a major cause age-related neurological pathology.

To test this in a clinically relevant model, we treated mice with daily doses of IPW, our lead TGFβ-blocking drug, and assessed a range of disease outcomes from cognitive impairment to seizure vulnerability. Mice given one week of daily IPW showed significant improvement in memory function. Furthermore, one week of IPW treatment drastically reduced the vulnerability of aged mice to induced decreasing seizure mortality at the given dose and decrease the severity of seizures when they occurred (unpublished).

Market analysis: Cognitive impairment affects 16 million Americans, and the number of people 65 and over diagnosed with dementia is expected to rise by 8.1 million by 2050. Cognitive impairment is costly, causing hospital stays that are three times more frequent than for other diseases. Dementia alone is estimated to be the third most expensive disease to treat in the United States. Medicare and nursing facility spending for individuals with Alzheimer’s disease is estimated at $847 billion. Unpaid care by family members is also a huge expense, estimated at 12.5 billion hours provided for a value of $144 billion. There are no disease-modifying treatments for dementia.

Our approach: Using Diagnostics to Guide Preventative Treatment

Bringing our preventative approach into clinical use entails a number of challenges, one of which is improving the diagnostic capability and understanding of who is at risk for acquiring cognitive decline and epilepsy. Considering our target market is post-traumatic epilepsy and dementia in aging, there is currently no way to diagnose risk or predict disease prior to onset of symptoms.
In identifying BBB dysfunction as a very early, initial event leading to later pathology, we are seeking to not only develop early preventative therapeutics, but also use BBB status as a diagnostic to predict disease onset; in other words, our research suggests that disruption of BBB should be a powerful, and previously unknown, predictor of future disease progression.

Seeking to realize the potential of such diagnostics, we developed a new imaging approach using contrast-enhanced MRI, combined with our proprietary software analysis, to detect disruption of the BBB (Figure 6). In this approach, the injected contrast agent is delivered IV and circulates through the blood. Normally, the contrast agent is excluded from the brain by the BBB, but when BBB is disrupted it leaks into the brain, where it is detected as an increase in signal intensity in MRI.

As proof-of-principle, we have tested this method in both of our target markets. In traumatic brain injury, we performed diagnostic imaging in American football players. These subjects represent a “mild” traumatic brain injury, in which repeated head hits can cause concussive injury yet are often not diagnosed and do not show any immediate clinical symptoms. We found, even in this very early stage of a mild head injury (prior to any disease), that football players show disruption of the BBB, whereas control patients show intact, healthy BBB (Figure 7). In the realm of age-related dementia, we performed imaging in aging patients exhibiting mild cognitive impairment (MCI). Importantly, MCI represents an early stage of disease, in which subtle cognitive impairment can be detected via neurological mental status testing, yet patients typically do not exhibit any strong deficits that interfere with their daily lives; as such it may be the earliest stage at which future risk for dementia can be currently detected. Here again at this early stage, we show BBB disruption in affected patients that is absent in healthy individuals (unpublished).

These data show that at the earliest stages that disease risk can be detected, patients already show a disruption of the BBB, demonstrating the potential of this diagnostic to identify at-risk patients before pathology progresses to a critical stage. In parallel with advancing our therapeutics, we are developing diagnostic software resources as a user-friendly, diagnostic package that can be used with existing MRI infrastructure, and which we will release as freely available, but also use BBB status as a diagnostic tool (source or freeware model). We believe that providing clinicians with the tools to diagnose BBB pathology will greatly improve understanding of when and how to prescribe our preventative therapeutics, providing a key step in improving patient outcomes by guiding treatment to the right patient at the right time. More broadly, we believe free availability of these diagnostics will greatly broaden the clinical understanding of the role of BBB pathology in causing disease, thus helping to contribute to a shift in clinical practices in which preventative approaches become the treatment norm.

Specific aims: to complete pre-clinical safety and proof-of-concept studies, positioning us to start clinical trials for preventative treatment in our target diseases.

Our studies to date have shown a very strong proof-of-principle: in rodents, treatment with our therapeutics is effective in preventing pathology arising from pathological, inflammatory TGFβ signaling, including gliogenesis after BBB disruption and cognitive dysfunction and seizure vulnerability in aging mice. These studies were performed in the academic context, and reveal the fundamental role of BBB pathology in causing neuronal dysfunction and neurodegenerative disease. In creating our start-up, Palsade Therapeutics, our primary objective has been to bring our innovative approach to market, and our main current goal is to raise early stage funding that allows a newly innovating company to pass its first milestones. In our case, while we continue to maintain a close partnership with the fundamental research in the lab of Dr. Danie-la Kaufer at UC Berkeley, external funding is critical for us to complete the necessary studies that are not performed in an academic context: the nitty-gritty proof-of-concept studies that are a key step in demonstrating the feasibility, and mitigating the risk, of taking this technology from the lab and towards clinical trials. These include characterization and validation of the drugs for clinical use (dosage studies establishing minimum effective dose, duration of treatment efficacy, etc) and safety studies (toxicology, side effects, etc).

We will complete these studies using a virtual business model via contract research organizations (CROs) specializing in preclinical studies. The CRO approach carries many advantages, and mitigates a number of risks, as follows: 1) CRO best practices adhere to robust pre-clinical standards and carry the inherent advantage of site replication. As such, validation of our therapeutics from an external CRO will provide compelling evidence to future investors, granting agencies, regulators, and other stake-holders of the overall efficacy of our drug portfolio. 2) As an early preclinical company, use of CROs will keep us lean and avoid any permanent infrastructure or personnel burdens at time when we are not expecting to generate revenue. 3) Contracting these preclinical studies will allow us to devote our sustained focus on the other key start-up milestones of our company; implementing strategy, securing funding, and developing partnerships towards clinical trials in a way that is necessary to establish the minimum effective dose of these drugs.
in preventing the target pathologies of epileptogenesis (PTE) and age-related cognitive decline, as well as frequency of dosing relative to the target disease. Establishing the correct dose will allow us accurately assess subsequent toxicology and avoid potential pitfalls of failing toxicology due to excessive dose.

SA1.2: Dosing for post-traumatic epilepsy. One strong advantage of our preventative therapeutic approach is that our therapeutics need only be given after acute injury, while BBB is disrupted, to prevent subsequent disease progression.

Specific aim 2: safety and toxicology

We included losartan in our patient filing to enable a potential path forward to dosing in rodent and non-rodent (dog) models, with cohorts of 3 males and 3 females, with specific focus on cardiovascular safety. Given that cardiovascular toxicity is frequently observed in preclinical studies of TGFβ antagonists, it is not recapitulated in human clinical use with small molecules or antibodies.29

2.2: Good Laboratory Practice (GLP) Toxicology. If our enabling studies are successful, we will proceed with GLP safety studies. Studies will be 4 weeks of drug administration (compared to controls) with subsequent recovery in rodent and dog. Under documented GLP practices, doses will be low (no adverse effect), clinical, and maximum tolerated, as optimized by the prior studies. Target endpoints will be general toxicology, including mortality, clinical signs, body weight, temperature, activity level, hematology, clinical chemistry, toxicokinetics, and pathology (complete battery of tissues).

Business Plan

A major strength of our company is our connections to the academic lab of Dr. Daniela Kaufer and the supportive institutional environment at UC Berkeley, which facilitates entrepreneurship spun out of academic research. Thus, while using external funding for preclinical studies, we are positioned to simultaneously advance other aspects of our business plan in parallel with the support of University resources. This allows us to move forward at very low costs and with unique resources bolstering our success. Key resources are as follows: (1) The academic research lab. All of our preliminary data was generated in the lab of Dr. Daniela Kaufer (Kaufer and Friedman), and these robust research programs will continue in parallel. In particular, future studies in progress include new clinical rodent disease models (TBI induced by weight-drop), rodent MRI to track BBB disruption and efficacy of treatment in vivo, and continuing human studies to test the predictive power of BBB diagnostics. These studies will provide key data supporting our approach, and are performed from academic funding sources (grants, foundations, etc.). The lab also provides us a partner for our future STRR grant (92 Entrepreneurship programs: We are enrolled in theQB3 Institute’s “Startup-In-A-Box” program, the Bakar Entrepreneurial Fellowship program, and in the SkyDeck incubator space. These programs give a vast array of resources to aid spin-out start-ups, including free FTO analysis and market analysis, SBIR/STTR workshops, dedicated support staff, and access to development events including a large network of investors and consultants. We are also enrolled in UC Berkeley’s “Methods of Technology Innovation” (MTB) program, a crash course in entrepreneurship and business models for STEM grad students outside of the traditional MBA program, taught by Prof. Ikilqan Siftn, Chief Scientist & Founding Director of the Sutardja Center for Entrepreneurship & Technology. (93) IP: UC Berkeley’s IP office (IP:IRA) allows us a free path to file new patent disclosures derived from lab discoveries, which will then be licensed to use for our exclusive use. This allows us to obtain IP protection for future disclosures at no cost (in particular we are developing alternate TGFβR blockers, now in the synthesis and testing phase, as risk mitigation in case our current approaches fail preclinical hurdles.

Conclusion

We are developing a novel approach to treat post-traumatic epilepsy and age-related cognitive decline. Unlike current therapies, our disease-modifying strategy attacks the underlying causes of neural dysfunction and has the potential to prevent, slow, and reverse the progression of disease. Building on over 10 years of our research showing a new link between vascular damage, TGFβ signaling, and disease outcomes, we are now working to bring this new therapy into the clinic by completing safety and toxicology studies. As an early stage venture, we face considerable risk, yet we have developed a risk mitigation plan supported by strong translational data in animal models, and human imaging diagnostics that not only identify the hallmarks of BBB pathologies in human patients, but also give us the capacity to deploy our drugs in targeted, personalized manner.

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56 57

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Abstract

The ease and abundance of knowledge acquisition that is unparalleled in history, renders knowledge transition and practicing of skills in education insufficient. The importance of personal reflection and identity, i.e. the individual’s mindset, is increasingly important. Re-thinking educational approaches, to entrepreneurship and leadership in particular, is important since they are activities for which perfect information cannot be gathered.

This paper introduces a new pedagogical approach that we will refer to as the MIND-methodology, which incorporates aspects of the individual’s mindset. The novel pedagogical approach includes four building blocks: theory practice, mindset and engagement-and-networking. The MIND-methodology is based on accepted pedagogical theories and known psychological aspects: social learning, communities of practice, and fixed and growth mindset. The novelty of the methodology lies in its clear student-centered approach and its focus on the student’s mindset.

The methodology has been used in ongoing education in entrepreneurship and leadership over the course of about 10 years, and is gradually evolving. The results from applying the methodology show promising results for the students also calls for the use of innovative models in teaching and may involve changing the content of courses as well as the process of learning itself.

To educate future entrepreneurs is orthogonal to traditional teaching in respect to how teaching is conducted. A leader/instructor that wants to educate innovators should e.g. lead from the side as opposed to lead from the top, should treat the group members as colleagues and not as a subordinate, etc. This is unconventional in teaching and learning situations and calls for a different mindset of the leader/instructor. It is essential for the students to be exposed to this mindset if themselves want to become leaders of future entrepreneurs, intra/interpreneurs or innovators.

Entrepreneurship and Leadership are two communities with their own strong cultures, i.e. there is an unformulated understanding of what it means to "be an entrepreneur or leader" or what it takes to "become and belong in the entrepreneurial or leadership communities". Traditional pedagogical approaches in teaching entrepreneurship are centered on theory and practice alone, whereas the mindset part, i.e. the "become and belong" aspect is often left out. The proposed new pedagogical methodology includes activities centered on the mindset of the students, helping the students to adapt their mindset to that of a successful entrepreneur/leadership culture.

The paper starts with a presentation of the theories that the MIND-methodology is based on. Next, the MIND-methodology itself is presented, the general overview, its four building blocks, and the whole ecosystem. A short presentation of the deployments of the MIND-methodology to an Entrepreneurship curricula as well as to a Leadership curricula are given and initial experience is described. The introduction of the MIND-methodology opens up for interesting research. Finally, the conclusions are presented.

Theories

Theory of planned behavior

The link between cognition and behavior has been explained by the Theory of Planned Behavior. Accordingly, behavior is preceded by the intention to do so. Behavioral intentions, in turn, can be predicted by three cognitive components, namely a) attitude, i.e. the person’s positive or negative evaluation of the behavior, b) subjective norm, i.e. the perceived social pressure from significant others to perform the behavior, and c) perceived behavioral control, i.e. the subjective evaluation of whether the individual can perform the behavior as well as its subjective ease or difficulty.

In the context of entrepreneurship, most individuals will only be motivated to start their own company if they think doing so is a good thing to do, whether at least someone in their personal network supports the idea and whether the individual thinks he/she has the time, resources, etc. to do so. Starting the company is not just the act of incorporation. Entrepreneurship is more complex than that. On the behavioral level, starting a company is the end result of dozens of previous steps and actions. Ideation, resource acquisition and pitching are only few examples of behaviors that are required to actually "start a company".

Each behavior in turn comes with its own combination of attitude, subjective norm and perceived behavioral control. Previous education has taught some students to ideate and create but not to sell or commercialize their products. In fact, on the level of subjective norms, traditional classroom settings have fostered a culture of risk-aversion. Through mechanisms such as multiple-choice testing, it has produced excellent students by rewarding rote-learning and compliance but often penalizing experimentation or risk-taking - behaviors that are crucial for entrepreneurship and innovation.

Fixed and growth mindset

In addition to the theory of planned behavior, the mindset of a person is critical to understanding the behavior he/she will engage in. Mindset constitutes a certain set of attitudes and beliefs and is therefore central to behavior.
A common distinction in mindset has been made between fixed and growth mindset 3. Accordingly, people with a fixed mindset believe that skills and ability reflect inherent traits that are stable. They build their identities around their level of ability. Research has shown, however, that this way of thinking exerts constraints on performance in the long-term. This is due to the fear these individuals experience when faced with challenges as they frame these situations as threatening. Due to their fear of failing or of losing they avoid taking on new challenges or entering situations where others can question their credibility. On the other hand, people with a growth mindset believe in the malleability of skills and ability. Moreover, they believe that success is the reflection of effort. For persons with a growth mindset, the reward comes from overcoming challenges and impossible situations. They feel internally rewarded for the process rather than the result. As they continuously take on new challenges they continue to grow and expand their skills and abilities 4.

Community of Practice

Theories from social sciences define the concept of Communities of Practice 10. Communities of practice are groups of people who share a concern or a passion for something they do and learn how to do it better as they interact regularly. Communities of practice can add value to an organization as they interact regularly. Communities of practice are an example of such a learning system, and belonging to such a community is essential to our learning. There are different ways of belonging to a community of practice; one of them is Engagement, i.e. the possibility to do things together with peers in the community, another one is Networking, i.e. to meet and spend time together with peers in the community. The way we engage and network in a community profoundly shapes our experience of who we are 11.

Building Block: Theory

By teaching and learning Theories, the students will acquire Knowledge. Knowledge is a familiarity, awareness or understanding of someone or something, such as facts, information, descriptions, or skills. The old Greek philosopher Plato famously defined Knowledge as "justified true belief" 6.

Examples of knowledge in the domain of entrepreneurship could e.g. be to be aware of various project management methods. Examples of knowledge in the domain of entrepreneurship could e.g. be to know the rules of giving a pitch to venture capitalists or the steps needed for developing a prototype, etc.

Building Block: Practice

By including elements focused on practice to the students, they will acquire skills. A skill is the ability and capacity acquired through deliberate, systematic, and sustained effort to smoothly and adaptively carryout complex activities or job functions involving ideas (cognitive skills), things (technical skills), and/or people (interpersonal skills) 4. In order to become successful entrepreneurs or leaders, students need to get opportunities to practice what they have learned. Alternative, by exposing them to realworld situations, they can learn vicariously, i.e. by watching others. In addition, constructive feedback should be provided on the performance in order to allow for more skill development.

Examples of skills in the domain of entrepreneurship could e.g. be to know how to adjust a company’s pitch story based on the audience. Examples of skills in the domain of leadership could e.g. be to have insights in how business models can be applied when taking strategic decision at corporate levels.

Building Block: Mindset

The cognitive antecedent of behavior represents the third element of the MIND-methodology and complements elements of Knowledge transmission and opportunities for practice. The mindset element underlines the importance of changing or confirming an individual’s mindset and thereby experiencing personal growth. Personal growth is a longitudinal journey for each student, a process that takes time to unfold. Personal growth implies gaining self-efficacy. Personal growth is always done on an individual basis but in support of others. Thus including personal growth in a curriculum therefore requires student-centered activities regarding their mindset, their thoughts, their beliefs and their goals. Personal growth incorporates “learning to become” and “learning to belong”, two components in the social theory of learning 10. The steps in this longitudinal journey are iterative and needs elements related to both Action and Reflection. Games are an example of an Action element and Learning Journals are an example of a Reflection element. Typical entrepreneurial behavioral patterns have been studied 1,7 as well as typical leadership styles 8.

Examples for personal growth in the domain of entrepreneurship can e.g. be to understand what additional characters you need in your team in order to complement your skills. In Leadership it can be the ability to define/articulate and to understand one’s own strengths and weaknesses, one’s own abilities and disabilities, etc.
In a two-year long leadership curriculum (Technology Management programme) the leadership-interested students at Lund University, Sweden, do not only learn about theory and practice, they also work hard with their own mindset in order to find their own strengths and weaknesses related to leadership. The main vehicle for working with the students’ mindset at Lund University is focused on Reflection and is referred to as Learning Journals. Learning Journal is a mean that, over a longer period of time, lets the students confirm or change their mindset by writing down their individual thoughts and thereby sorting out their own beliefs. The method is referred to as Lund Learning Leadership Method (3LM) 14.

Student reports and placement reports reveal promising results linked to the inclusion of the mindset perspective. The students in the Leadership curriculum at Lund University, claim that the curriculum helps them grow both as individuals and professionals in a way they would not have done without the mindset activities. Five to ten years after graduation, the students rank the mindset by writing down their individual strengths and weaknesses related to leadership. They are growing both as individuals and professionals.

Summary

This paper presents the MIND-methodology, a novel pedagogical approach for teaching and learning Entrepreneurship and Leadership. The novelty of the methodology lies in its clear student-centered approach and its focus on the student’s mindset. It is based on accepted pedagogical theories and known psychological aspects, social learning, communities of practice, and fixed and growth mindset.

The MIND-methodology includes four building blocks: Theory, Practice, Mindset and Engagement-and-Networking, see Figure 1. The first building block, Theory, stresses the learning of theory and thereby acquiring knowledge, the second building block, Practice, highlights the importance of practicing and thereby getting skills, and the third building block, Mindset, underlines the importance of changing or confirming an individual’s mindset and thereby experiencing personal growth. The fourth building block, Engagement-and-Networking, is supporting the other three and is a mean for improving the students’ self-efficacy, and enabling scalability of the curricula/program.

The MIND-methodology is strongly student-centered (adjusted for each individual), has an action-reflection iterative approach, and has already generated preliminary and promising results in entrepreneurial-leadership curricula. Our main hypothesis is that by applying the MIND-methodology to curricula, additional value is provided to the stakeholders (i.e. students and their future companies or employers). The introduction of the MIND-methodology for teaching and learning Entrepreneurship and Leadership also opens up for many interesting research questions.

References


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