MEDSCI 9508

February 10, 2025

Lecture 1: scientific consideration in translational science

Presession task

**Main Theme**

The paper discusses the persistent issue of translational failure in stroke research, where promising preclinical treatments fail to be successfully applied in clinical settings. Despite over a thousand successful preclinical studies, only two have translated into clinical practice, highlighting a "translational block." The authors critically analyze current methodologies, compare stroke research with other medical fields, and suggest an "out-of-the-box" approach to improve translation.

**Key Points & Notes**

**1. The Problem of Translational Failure in Stroke**

* Stroke remains the **third leading cause of death** in industrialized countries.
* **>1000 preclinical studies** in acute stroke research, yet minimal clinical success.
* Failure occurs due to weak preclinical evidence, inappropriate models, and poor methodological rigor.

**2. Challenges in Stroke Translation**

* **Mismatch Between Preclinical and Clinical Models**
	+ Preclinical stroke models use **young, healthy rodents**, while clinical patients are **elderly with comorbidities**(e.g., hypertension, diabetes).
	+ Rodent models often receive interventions **immediately after stroke onset**, while human patients face **significant treatment delays**.
	+ The rodent stroke "patient" is well-controlled, while human stroke is unpredictable and heterogeneous.
* **Differences in Experimental vs. Real-World Settings**
	+ Stroke patients receive **multiple medications, secondary prevention strategies, and supportive care**, which are missing in preclinical models.
	+ Human stroke trials recruit **patients with mild symptoms**, introducing a selection bias.
* **Scientific and Methodological Pitfalls**
	+ Lack of **randomization, blinding, and proper control groups** in preclinical studies.
	+ Publication bias: **negative results are rarely published**, creating an illusion of success in stroke research.
	+ Low compliance with guidelines (e.g., **ARRIVE, STAIR, STEPS, RIGOR**).
	+ Underpowered studies with **small sample sizes**, leading to exaggerated effect sizes

**3. Lessons from Other Fields**

* **Hypothermia as a Case Study**
	+ Hypothermia was effective in **neonatal hypoxic-ischemic encephalopathy (HIE)** but failed in **ischemic stroke**.
	+ **Key differences**: Stroke involves more complex **secondary injury cascades**, and the **timing of hypothermia** in stroke trials was often delayed.
* **Comparisons with Cardiology (Myocardial Infarction)**
	+ Similar translational failures exist in **cardioprotection research**.
	+ Cardiovascular patients have **comorbidities, polypharmacy**, and variability in myocardial salvageability, affecting trial outcomes.
* **Success in Multiple Sclerosis (MS)**
	+ The **experimental autoimmune encephalomyelitis (EAE) model** has been successfully translated into MS treatments.
	+ MS therapy benefits from **clear biomarkers, long-term treatment windows, and well-defined patient stratification**—elements missing in stroke research.

**4. Proposed Solutions for Stroke Research**

* **Rethinking Stroke as a "Chronic, Relapsing Vascular Disease"**
	+ Stroke should be viewed beyond acute events—considering **long-term neuroprotection and secondary prevention strategies**.
* **Improving Preclinical Models**
	+ Use **middle-aged or older rodents** with relevant **comorbidities**.
	+ Introduce **polypharmacy and environmental factors** to better mimic human conditions.
* **Better Trial Design**
	+ **Stricter adherence to ARRIVE, STAIR, and STEPS guidelines**.
	+ Use **larger animal models (e.g., non-human primates, pigs)** where feasible.
	+ Define **effective patient stratification** and **realistic treatment windows** in clinical trials.
* **Interdisciplinary Collaboration**
	+ Closer interaction between **preclinical and clinical researchers, industry, and regulators**.
	+ Encourage **replication studies** to validate findings before clinical translation.

Lecture notes

* Benefits of science research
	+ Health
	+ Economic
	+ Knowledge
	+ Environment
	+ Technology

What is translational science

* NIH National center for advancing translational science, translation is the
	+ Process of turning observation in the laboratory clinic, and community into interventions that improve the health of individuals and populations- from diagnostics and therapeutics to medical procedures and behavioural interventions
* There is translation from the bench to the bedside a from the bedside to the bench

Translational science blocks

* T0 Basic science research
	+ Tip of the iceberg
	+ Translating clinical insight and relevant constraints into the pre-clinical studies with the goal of improving t1 studies
* T1 Translation to humans
	+ Huge divide from T0 to T1
	+ Translation of bench research into demonstrated effects for patients
* T2 Tralation to patients
	+ Translation from studies if treatments into usual clinical care
* T3 Translation to practice
	+ Implementation and dissemination into wide use
* T4 Translation to community
	+ Translation into impact on the public health and public policy

Early success: chemotherapy

* Paul Ehrich pioneered the search for a chemical that would kill a microorganismal AND leave the host unaltered—the magic bullet

Salvarsan

* In 1901 Ehrlich developed a new derivative of arsenic compound, which the code-named compound 606 (the number representing the series of all his tested compounds) the compound was effective against malaria infection in experimental animals
* in 1905, Fritz Schaudinn and Erich Hoffmann identified a spirochaete bacterium
(Treponema pallidum) as the causative organism of syphilis.
* With this new knowledge, Ehrlich tested Compound 606 (chemically arsphenamine) on a syphilis-infected rabbit. He did not recognise its effectiveness. Sahachiro Hata went over Ehrlich's work and found on 31 August 1909 that the rabbit, which had been injected with Salvarsan 606, was cured using only a single dose, the rabbit showing no adverse effect.
* The normal treatment procedure of syphilis at the time involved two to four years routine injection with mercury. Ehrlich, after receiving this information, performed experiments on human patients with the same success.
* After convincing clinical trials, the compound number 606 was given the trade name Salvarsan and was commercially introduced in 1910!

Penicillin

* Alexander Fleming, a bacteriologist at St. Mary’s Hospital, had returned from a vacation when, while talking to a colleague, he noticed a zone around an invading fungus on an agar plate in which the bacteria did not grow.
* After isolating the mold and identifying it as belonging to the Penicillium genus, Fleming obtained an extract from the mold, naming its active agent penicillin.
* Fleming published his findings in 1929. However, his efforts to purify the unstable compound from the extract proved beyond his capabilities.
* For a decade, no progress was made in isolating penicillin as a therapeutic compound.
* During that time, Fleming sent his Penicillium mold to anyone who requested it in hopes that they might isolate penicillin for clinical use.
* Good trainee: At Oxford University, Ernst Chain found Fleming’s 1929 article on penicillin and proposed to his supervisor, Howard Florey, that he try to isolate the compound.
* In 1939, Howard Florey assembled a team, including a fungal expert, Norman Heatley, who worked on growing Penicillium spp. in large amounts, and Chain, who successfully purified penicillin from an extract from the mold.
* Florey oversaw the animal experiments. On May 25, 1939, the group injected 8 mice with a virulent strain of Streptococcus and then injected 4 of them with penicillin; the other 4 mice were kept as untreated controls.
* Early the next morning, all control mice were dead; all treated mice were still alive. Chain called the results “a miracle.” The researchers published their findings in The Lancet in August 1940.
* In February 1941, the first person to receive penicillin was an Oxford policeman who was exhibiting a serious infection with abscesses throughout his body. The administration of penicillin resulted in a startling improvement in his condition after 24 hours. The meager supply ran out before the policeman could be fully treated, however, and he died a few weeks later.

Thalidomide

* Thalidomide is a sedative drug discovered at the end of the 50s, which caused a worldwide tragedy.
* The drug has been prescribed to many pregnant women in order to relieve pregnancy nausea. It was later found that thalidomide caused irreversible damages to the fetus and thousands of children were born with severe congenital malformations. Many of them did not survive more than a few days after they were born.

Discovery of thalidomide

* Thalidomide was initially selected as “Candidate K17.” It was discovered from peptide research but promoted as being structurally related to barbiturate with hypnotic properties, beyond those of the classic barbiturate Luminal, but without toxicity.
* Thalidomide was first synthesized in 1954 in Western Germany by the firm Chemie Grünenthal, who found out that thalidomide had interesting sedative effects. Thalidomide appeared as a promising alternative to barbiturates that were then used as sedatives, because it didn’t seem to be toxic nor have any side effects. An overdose would only cause deep sleep, as opposed to barbiturates which could cause death if taken in excessive quantity.

Thalidomide as a hypnotic – animal model for sleep

* In the 1950s, simple tests in animals for hypnotic activity were available to evaluate thalidomide including “righting reflex” and “wheel running.” Thalidomide proved negative in both of these simple tests leading to the introduction of more complex and variable tests, a case of attempting to make the results fit the hypothesis. Chemie-Grünenthal finally used a complex “jiggle cage” test, involving cages of mice suspended over baths of sulphuric acid; movement of the cage dipped cathode electrodes into the acid thereby creating hydrogen gas. On the basis of a treatment-related reduction in hydrogen gas production, claim for hypnotic activity was made (and accepted)

Prescribing Thalidomide

* Thalidomide was marketed in 1956 by Chemie Grünenthal in Western Germany, first as an anti-flu, then in 1957, as a hypnotic drug. It was then available without prescription. In April 1958, thalidomide was marketed in the United Kingdom by Distillers Company. Several countries followed suit, and thalidomide was put into circulation under many different brands. Overall, thalidomide was sold under about 40 different names around the world, principally in Western countries and in Japan. Important advertising campaigns were led by its fabricants, starting with Chemie Grünenthal and Distillers Company. Thalidomide was described as a miracle drug. Thousands of samples were distributed to doctors, who were encouraged to prescribe it to pregnant women in order to alleviate pregnancy nausea. Everyone was told that this drug represented no risk at all for pregnant women.

Thalidomide
(<http://thalidomidestory.com/story/about-grunenthal/company-history/sales-at-all-costs/> )

* *“What the public did not know is that Grünenthal had no reliable evidence to back up its claims that the drug was safe. They also ignored the increasing number of reports coming in about harmful side-effects as the drug was being used. In fact, starting in 1959 Grünenthal was flooded with complaints from doctors about mild to severe and sometimes permanent nerve damage, especially by elderly people who had used the drug as a sleeping aid.*
* *The company was equally dismissive of concerns related to deformed babies. The drug was widely promoted as an anti-nausea drug for pregnant women experiencing morning sickness. When the company was confronted with reports on malformed babies and suggestions that the malformations could be possibly linked to Thalidomide, they didn’t react. Instead of taking all those reports seriously Grünenthal responded with measures to keep the drug on the market.”*

Was it just the times?

* The metabolic profile of thalidomide was never established, and it is often claimed that this was normal for the time.
* In the 1972 book “Thalidomide and the Power of the Drug Companies”, John Thierch, Dept of Pathology, University of Washington Medical School, Seattle is quoted as stating that “in the 10 years preceding the appearance of thalidomide no less than 25 compounds were shown by investigators ranging from Japan to the USA, to England and France to affect the fetus in utero, either killing many fetuses or inducing malformations….”. Therefore, the concept of drug induced teratogenicity was apparent at the time of thalidomide, but animal testing was not mandated.

Testing for teratogenicity

* Subsequent to the development of thalidomide, fetal malformations have been produced in rabbits and primates at high doses, and while rats are relatively insensitive, embryo lethality and fetal malformations (skeleton and eyes) have been reported in that species. Stabilizing the thalidomide structure by substituting one methylene group with a carbonyl group (increasing the half-life from 2.5 to 37 h) resulted in a greater teratogenic potency in rabbits, monkeys and rats; the malformations being the same as those produced with thalidomide.
* Although, in the 1950s nonclinical safety testing was limited to rodents, with appropriate testing, malformations could be produced in that species and resorptions were a known indicator of possible teratogenesis. The separation of response in rats and rabbits with thalidomide formed the basis for reproductive toxicology guidelines used today.

Animal Models of Disease

* One needs a method to study the pathophysiology of disease without harming patients.
* Although disease processes may not be the exact same in animal and people and treatments may have different toxicological and therapeutic properties in different animals there are not many alternatives.

First in man studies:

* First-in-human (FIH) clinical trials are the initial Phase 1 studies
* They are most often performed with healthy volunteers. However, if drug candidates that present serious health risks are investigated, such as certain antitumor drugs, patients who cannot readily benefit from the available therapies are assessed.
* a multidisciplinary team conducts FIH trials, including a clinical pharmacologist, a safety physician, a formulation scientist, a clinical development scientist, a clinical operation specialist, a toxicologist, and a regulatory affair specialist.
* Preclinical Road map:Early Product Development

Clinical Trial – Phase I

* conducted in a small group (~20-50) of individuals to determine an investigational drug’s safety and adverse effects and identify its appropriate dose.
* Early Phase 1 clinical trials provide data on the safety of drug candidates in humans, as well as indications regarding their mechanism of action.
* More advanced Phase 1 clinical studies deliver further data on the pharmacological effects of the drug candidate in humans, its metabolism, adverse effects associated with dose acceleration, and possibly early effectiveness data.

Clinical Trial – Phase II

* In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed.
* Because the sample size is small (generally **less than 50 patients**), Phase II clinical trials are only able to detect a large treatment improvement, e.g. greater than 10%.

Clinical Trial – Phase III

* A study that tests the safety and how well a new treatment works compared with a standard treatment.
* For example, phase 3 clinical trials may compare which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase 3 clinical trials only after they meet the goals of phase 1 and phase 2 clinical trials.
* Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve **300 to 3,000** participants.

Clinical Trial – Phase IV

* **A type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market**.
* These trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time.

Animal models of disease

* At the heart of the justification for the use of animal models of disease is that all organisms share some degree of (genetic) relatedness due to common ancestry.
* Construct validity: Is it the same cause (etiology) as in humans?

Face Validity: Does it look the same as in humans (same pathology and symptoms etc.).

Predictive Validity: Is there similarity in treatment?

What makes a good model of disease?

* Why so much failure?
	+ Two directional blocks:
1. Failure of preclinical treatments to reach clinical practice
2. Failure of clinical advances to reach preclinical models

Comparison of the “patients”

* Age
* History
* Stroke onset, duration, mechanism, heterogeneity
* Post-stroke care, reperfusion, drug support,
* Post-stroke patient evaluation

Why so much failure?

* The wide heterogeneity of types of clinical stroke, in terms of size, location, time-windows, degrees of reperfusion or collaterals, comorbidities, and the presence or not of salvageable penumbra, may eventually be the main reason for translational failure (Howells et al., 2010).
* Taking the problem to the level of organisms, it is fact that humans and rodents do have many similarities and hundreds of conserved molecular/genetic pathways in common as mammals (for an extensive review see Dirnagl and Endres, 2014), but
	+ Genetics
	+ Size (mouse brain 5 cm3; human brain 1500 cm3)
	+ Amount of gray matter (10% mouse : 50% human)
	+ Age used in model

Hypothermia as a treatment for stroke

* Methodological problems alone probably do not suffice to create translational block, because they also exist in research fields that translate successfully.
* Hypothermia failed translationally in acute ischemic stroke (negative story) (Kuczynski et al., 2020) but succeeded in brain hypoxia after cardiopulmonary resuscitation (positive story).

Experimental Autoimmune Encephalomyelitis (EAE) and Multiple Sclerosis (MS)

* EAE led to the development of multiple drugs for MS that control its inflammatory component yet studies on EAE face the same severe methodological and bias problems as stroke studies publication bias, insufficient sample sizes, and statistics, lack of blinding and randomization procedures, lack of multicenter studies, lack of validation studies ……
* The immune system for mice and humans very similar
* EAE and MS share pathological pathways
* Patients are similar (young, no pre-existing conditions or comorbidities)
* Extended incubation time for interventions

Hope?

* Brightside conclusion:
* the translational block seems to arise when we try to restore/treat cellular degeneration. In other words, it seems easier to succeed translationally when treating a disease target outside of the blood-brain-barrier, in a preventive manner, with an extended therapeutic time window and in young subjects without comorbidities.

Ways to improve likelihood of translation in stroke

1. preclinical testing of drugs on human tissue, after initial screening in rodents.
2. "humanize" our rodent preclinical models
	* 1. Humanize the immune system with BM transplants
		2. Humanize key genes
3. Recent studies indicate that preclinical inbred and SPF rodents fail to recapitulate a normal "dirty“ human environment due to their poor and altered microbiome, mycobiome, and virome.
4. drug discovery pipeline in stroke should include at least one validation study of the results in aged animals

Example Traumatic Brain Injury –

* Consistent injury
* Consistent subject
* Molecular, cellular tissue and behavioral analyses

Models of TBI

* In vitro systems – lack the complexity to study TBI, that should include the inflammatory and immune responses and manifests with complex pathologies that involve a variety of cell types in the brain culminating in behavioral problems.
* Animal models – yes but how well will a study in an animal reflect the human condition?

**Face validity** refers to how well an experimental model resembles the human disease it aims to replicate, based on anatomical, biological, and pathological similarities. The **Surgical Destabilization of the Medial Meniscus (DMM) model** is widely used in preclinical studies of **osteoarthritis (OA)**, particularly in rodents, to study joint degeneration mechanisms and evaluate potential treatments.

**Construct validity** refers to how well an experimental model accurately represents the biological mechanisms and disease processes seen in humans. A model with strong construct validity should closely mimic the underlying causes and progression of the disease it aims to replicate. The **Surgical Destabilization of the Medial Meniscus (DMM) model** is widely used in osteoarthritis (OA) research, particularly in rodents, to study the structural and molecular changes associated with joint degeneration.

**Predictive validity** refers to how well an experimental model can predict treatment outcomes in human disease. In the context of **osteoarthritis (OA)**, a model with strong predictive validity should accurately forecast the effects of potential **therapeutic interventions**, including **pharmacological, biological, and surgical treatments**. The **Surgical Destabilization of the Medial Meniscus (DMM) model** is commonly used in **preclinical OA research**, but its ability to predict treatment responses in humans has both strengths and limitations.

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Class 2

February 12, 2025

Lecture notes

Character

* What do you read
* D you have a narrow focu
* Do you ask questions
* Can you identify problems
* Are you a clear thinkier

Prepare

* Build a knowledge abse
* Read more than narrow focus
* Meet and dicuss ideas with indidviuals from other diciplines
* Be curious and ask questions

Problem to solve

* Problem statement
	+ Need to understand the language of the field
	+ Need to understand core issues
	+ Need to understand the limitations
	+ Neeed to articulate the key essence of the problem
* Key to finding a solution

Innovative appproachers

* Initiated by the problem that needs solcibg or indidvual curiosity
* To solve problem – need to decompose problem and arrange/replce compoenents in different wasys to discover new associations
	+ Team based
		- Social phenonmen that relies on interactions among knwolegdeable indidvuials
		- Requires creativity driven leadership
		- Requires collegial, trusting team
	+ Personal based
		- Creative insight or an ‘AH’ experience – novel idea or solution to a problem in the mind of an individual
			* Associative vs analystical thinking
			* How to achieve ‘AHA’ moment

Inspiration

* Most difficult aspect of pipeline
* Need to assemble multiple facts
* Lateral thinking
* Personal/team ‘AHA’ moment
* Find a way to let ideas percolate
* Try lateral thiking
* With others: try ideas with someone who is open minded nd innovative
* Alone; quiet time, go for a walk, drive

Seed

* Cant find innovative solutions if problem is not clear
* Need to formulate problem
* Need to understand limittaions, conditions
* Need info from users or targets of innovation

Recognize

* How to speate good idea from not so good idea
* The best ideas are obvious after describes
* Need knowledge: own, others experts
* With knowlfg, get confidence in own ideas and path

Nuture

* Many good ides go underveleoped or developed by others
* Need suitable environment to develop ideas
* Need experize: own plus others
* Need ability to build and work as part of a team
* Be ready to explore and fail

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Class 3

February 18, 2025

Lecture notes

**Innovation, Entrepreneurship, & Commercialization**

* **It’s about People**
	+ People create and bring new ideas to market
	+ Innovation and entrepreneurship are processes; they can be taught and learned
	+ It takes a community to create a culture of innovation, entrepreneurship, and commercialization
	+ Get involved, be part of the community

**Creators, Inventors, Entrepreneurs**

* Our goal is to create a community and culture that supports innovation, entrepreneurship, and commercialization
* **Commercialization:** Move new ideas from research out to the world
* Minimize barriers and provide supports (education, services, opportunities)
* This fits within the educational mandate of Universities and provides career alternatives to trainees
* It provides local and regional economic impact
	+ **BioNext:** >60 companies; 400 jobs; $100M in enterprise value

**Innovation, Entrepreneurship, & Commercialization**

**Innovation (Institutes)**

* Research the big questions of our time
* Create and validate new inventions
* Early prototypes and proof of function
* Early IP Generation

**Entrepreneurship (Morrissette)**

* Develop a sustainable business model
* Inspire team and stakeholders (mission and vision)
* Create and build a team
* Finance, HR, and communication

**Commercialization (Incubators)**

* A form of knowledge mobilization
* Bring an Innovation to Market
* Define and manage the parallel tracks of development (Product, IP, quality, regulatory, clinical, etc.)
* Early company creation

**Incubators, Accelerators and Supports**

**MedTech Incubator**

* State-of-the-art prototyping and testing facility
* Connections to research & preclinical development expertise
* Connections to the clinical research community (KOLs)
* An expert network for MedTech development & commercialization

**Morrissette**

* Entrepreneurship programming across the Institutes
* Maker spaces
* Business advisors
* Event Space
* Morrissette Accelerator (cohort-based programs)
* Demo Day (Investors)

**AGENDA**

* **Innovation and Entrepreneurship**
* **Create something of Value**
* **Market Assessment (Competitive Analysis)**
* **Product Market Fit**
* **Dig a Little Deeper (Development and Commercialization)**
* **Reimbursement**
* **Value Statement Exercise**

**Value Drives Adoption**

**Hurdle Description**

* E.coli O157 produces a toxin that can lead to kidney failure and death (Walkerton ON, 2000).
* E.coli O157 is found in cattle, it does not cause disease but serves as a reservoir for shedding into the environment that leads to contamination of water and agricultural crops.
* A scientist at UBC (Dr. Brett Finlay) invented a vaccine to prevent E.coli colonization in cattle and licensed the technology to a biotech company (Bioniche).

| **Science/Technology** | **Technology works, vaccine prevents E.coli 0157 colonization** | **✅** |
| --- | --- | --- |
| Manufacturing | Built GMP Manufacturing Plant (>$25M) | ✅ |
| Regulatory | Field trials in cattle showed safety and efficacy and received Canadian Food Inspection Agency approval | ✅ |
| Sales/Marketing | No market for the vaccine, no one will pay for its use | ❌ |
| Research / IP | Enterohemorrhagic Escherichia coli vaccine (US Patent US7300659B2) | ✅ |

**Value Drives Adoption**

* The best technology, best development strategy, and best team, cannot overcome the absence of a paying customer
* **Create something of Value**
* **Create something needed in the Market**

**Design Thinking Framework**

1. Understand customer’s journey
2. Define the Problem/Need
3. Define the customer segments
4. Validate the Need in the Market

**Commercialization is Risky**

* **Technology is cool; people love how it works**
* **Technology Risk:** Is it Feasible, does it work, can it be made, etc.
* **Execution Risk:** Do you have the right team?
* **Market Risk:** The cause of most startup failures

**Product – Market – Fit**

* **New Technology**
* **Problem / Need**
* **Customer / Market**
* **Value Proposition**

**General Market Assessment Tools**

* **Google:** (Google Patents)
* **Primary Publications (PubMed):**
	+ Incidence of disease/condition, Economic Analysis of the Problem, Pharmaco-economics of treatments, Consensus on treatment methods
* **General Market Research Reports**
* **UWO Library Databases:**
	+ BCC Research, Frost & Sullivan, IBIS World, Pitchbook

**Market Assessment Programs**

* **Lab2Market Programs for trainees (researcher-entrepreneur)**
	+ **L2M Discover**: Is entrepreneurship for me?
	+ **L2M Validate**: PMF for my idea
	+ **L2M Launch**: Create a business model and then a startup
	+ **L2M Build**: Product development
* **Primary Market Research**
	+ Talk to your Customer (stakeholders, KOLs, regulators, partners, etc.)

**Example: Exubera**

* **Exubera™ = inhaled insulin (injectionless)**
* **FDA approval January 2006 (Pfizer and Nektar)**
* **Pfizer predicted it would bring in $2 billion a year in sales by 2010**
* **Analysts expected copycats to turn inhaled insulin into a $5 billion annual market**
* **Injections are minor, accurate, and discrete**
* **Accurate dose levels and adjustments difficult with Exubera**
* **Exubera was 30% more expensive with no clinical benefit (higher co-pays)**
* **Actual worldwide sales $4M (no significant uptake)**
* **Halted Program (Oct 2007), wrote-off $2.8 Billion**
* **Mankind repeated this process 2013-2016**
* **What Problem was being solved?**

**Market Landscape Assessment (PMF)**

| **Problem/Need** | **Customer** | **Technology/New Solution** |
| --- | --- | --- |
| What is the problem to be addressed? What is the unmet need? | Who has this problem/need? What is the size of this market (Customer #s, not $s)? | Does technology work? Does technology solve the unmet need of the customer? |

**Competitive Analysis**

* How is the problem currently solved?
* Do all customers use the same existing solutions?
* Have some created their own solutions?
* How is the new solution superior to existing solutions?
* Does it fit into Customer’s Work-Flow?
* Who provides current solutions?
* "Customer-driven forecasting" (#customers/year)
* **IP Status (landscape)?**
* **Reimbursement?**

**Value Prop Validation**

* Do customers value the new solution over the existing solutions enough to adopt the new solutions?
* Why? What advantage does it provide?

**Business Model Canvas**

| **Key Partners** | **Key Activities** | **Value Proposition** | **Customer Relationships** | **Customer Segments** |
| --- | --- | --- | --- | --- |
| Partners & Suppliers | Create, test/validate business model | Is the Problem Real? Do you solve the Problem? Superior to existing solutions? Does anyone care? Who has the problem? | Get, Keep, and Grow Customer #s and value | Define customer segments. What are the numbers? Bottom-up market analysis. What is the customer journey? Who drives buying decisions? What drives adoption? |

| **Key Resources** | **Channels** | **Cost Structure** | **Revenue Streams** |
| --- | --- | --- | --- |
| Physical, Financial, Human, Legal (IP, HR, contracts) | How do you reach your customers? | Must show that Costs < Revenue at some point. Model Costs, Milestones, and Timelines. Burn Rate (monthly); Cash on hand (when do you run out). | What is revenue strategy for each customer segment? Pricing Tactics: value vs cost? |

[Business Model Canvas Primer](https://www.youtube.com/watch?v=QoAOzMTLP5s&t=1s)

**Pitch: Creative Destruction Lab**

**CDL Session 1: A 90-sec Pitch**

1. **Captivate with a great introduction (10 seconds)**
	* Don’t waste time with names, let the audience feel the pain or get their curiosity (with the problem/unmet need)
2. **State the problem (25 seconds)**
	* Show your homework, some stats, the impact of the problem on the customer (and the need for a new solution)
3. **Discuss the solution (20 seconds)**
	* Introduce yourself, your idea (solution/technology), how you will solve the problem.
4. **Evidence of the market (customer) (20 seconds)**
	* Who is your target market, why them, value prop vs existing competition
5. **Wrap it up with a great closing line (15 seconds)**
	* Create desire, a sense of value, you don’t want to miss this opportunity (tell me more)

**OK, Now What?**

* You have identified an unmet need in the market
* Your product works to solve the problem/fill the need
* You have identified the first customer segment
* You have validated the value proposition with the customer and confirmed you have Product-Market-Fit
* **Now What?**
	+ **Dig a little deeper**

**I-Corps: NIH entrepreneurship training program**

* For companies that received SBIR or SBTT funding from NIH or CDC.
* An 8-week, hands-on program, to focus on your business plan and get the tools to bring your treatment to the patients in need.
* **Talk to 100 stakeholders to address the following:**
	+ Define core customers and value proposition (PMF)
	+ Define your IP and regulatory strategies (and risks)
	+ Understand your path to market (partnerships, collaborations, commercialization pathways)
	+ Identify suitable financing vehicles

**Development & Commercialization**

* **Intellectual Property**
* **Product Development**
* **Quality Management**
* **Regulatory Strategy**
* **Product Standards & Compliance**
* **Commercial Manufacturing**
* **Go To Market Strategy (Reimbursement)**
* **Financing, Business Model; Team Building**

**Intellectual Property**

* **First determine your business model**
* **Then determine the IP strategy that supports the business model**
	+ What is the role of IP in your business model?
	+ IP: Patents, trade-secrets, copyright, and trademarks
* **Patents:**
	+ Patentability: Utility, Novelty, Obviousness
	+ Strategy: Protect composition, method of use or manufacture, improvements, design, and brand.
* **Know your competition and whether you infringe other IP (freedom to operate).**
* **Patent provides a right to commercially exploit an invention**
	+ A right that can be bought, sold, and licensed for use

**The Value Statement Exercise**

* Typically has three components:
	1. **What is the product or service?**
	2. **Who is the customer/user?**
	3. **What value does it provide to the customer?**

**Example: Nitinol alloy (nickel-titanium)**

* **Super-elasticity and shape-memory properties**
* **When formed into a coronary stent, the added flexibility assists in coronary artery placement, while shape memory helps to hold the artery open.**
* **The Nitinol stent allows the interventional cardiologist to provide to their cardiac patients a life-saving treatment alternative to open-heart bypass surgery, as a minimally invasive, outpatient procedure.**

MEDSCI 9508

Class 4

February 19, 2025

Lecture notes

**Pitch Deck 101**

The goal of the pitch deck is to give a snapshot of your story and investment opportunity!

* **Problem**
* **Competitors**
* **Solution**
* **Customers**
* **Market Potential**
* **Team & Backing**
* **Go-To-Market**
* **Financial Plan**
* **Key Milestones**
* **Business Model**

**What is Entrepreneurship?**

**Entrepreneurship is about opportunity identification and problem solving.**

Every successful venture **solves a clearly defined market problem**.

Why does this matter?

* How does an entrepreneur **approach value creation** through problem solving?

**Understanding The Problem**

**Problem Identification**

We are going to help (**Describe the Segment**), who are dealing with (**Describe the Problem**), which matters because (**Why Does it Matter?**). This problem exists because (**Root Cause of the Problem**).

**Problem Compellingness**

* Describe the **pain point of the consumer** backed by compelling data.
* How does the **customer currently address the problem**? Are there **gaps** in those solutions (**Think Leon’s vs. Ikea**).
* Quantify the **impact of not solving the problem** (**Money, Time, Wellness**).

Every successful venture **starts with a clearly defined market problem**.

**Empathy For The Consumer**

**Identifying Opportunity Segmentation**

* **Behavioural**
* **Psychographic**
* **Demographic**
* **Geographic**

**When Developing a Solution, ASK…**

1. Could we **Define a Customer Persona**?
2. Do we **Understand their Alternatives**?
3. Do we **Know their Customer Journey**?

What **new or layered problem** do you want to solve **faced by the consumers you have identified**?
Why should you care?

**London, Ontario… 1983.**

Same Brand
Same Test Market
Same Timespan

The **best branding and advertising in the world** does not sell a solution if the solution does not **provide inherent value to the stakeholder**.

**Competitive Analysis**

* **List Direct Competitors and Subs**
* **Highlight Gaps in Competitor Offering**
* **Barriers to Entry?**
* **Why You, Not Them?**

**The Solution - Your Value Proposition**

A good frame will summarize the organization’s **target consumer, value proposition, and competitive differentiation**.

Among **[target market]**, **[brand name]** is the brand of **[frame of reference]** that **[point of difference]** because **[reason to believe]**.

* **Why does your business exist?**
* **What makes people want to come to your business over competitors?**
* **How can you integrate storytelling to connect with the audience and drive home your value proposition?**

**Market Potential**

**Sizing the Market**

* **Total Addressable Market (TAM) =** Total Population \* Average Selling Price
* **Serviceable Addressable Market (SAM) =** TAM \* % Market Share Capture
* **Serviceable Obtainable Market (SOM) =** SAM \* Adjusted Market Penetration

**Questions to Consider:**

* Who are you **catering to**?
* What are the **external forces** driving this segment?
* **SWOT? Changing trends? New technologies? Political influences?**
* **Projecting Growth**

**Team & Backing**

**Establish Credibility.**

| **Role** | **Key Experience** | **What Do They Bring?** |
| --- | --- | --- |
| Role 1 | Experience 1 | Contribution 1 |
| Role 2 | Experience 2 | Contribution 2 |
| Role 3 | Experience 3 | Contribution 3 |

**Go-To-Market**

* **Marketing Plans**
	+ **Product | Price | Promotion | Place**
	+ **Market share? Payback? CAC?**
* **What is your Plan for Execution?**
* **What are some Projected Outcomes?**
* **Sales Plans**
	+ How will you **communicate your solution’s value** to the target market?
	+ What **distribution method** is most effective?
* **Partnership Plans**
	+ What are the **gaps** in your organization’s capabilities?
	+ What **partnerships** are established to align with the strategy of the firm?

**Business Model**

* **Revenue Model**
* **Pricing Model**
* **Account Size/Value**
* **Sales & Distribution**
* **Customer Pipeline**

MEDSCI 9508

Class 5

February 24, 2025

Education & Career

Western Innovation and Strategic Partnerships

100 Collip Circle, Mogenson Building, Suite 200, Western Research Parks, Western University

Western Technology Transfer Office helps researchers protect and commercialize their innovations through patents, licensing, and spin-off companies.

Strategic Partnerships build industry and community collaborations in areas like sustainability, smart systems, and neuroscience.

Western Research Parks provides space and resources for startups and research-driven businesses.

Together, these teams turn ideas into real-world impact, support economic growth, and create opportunities for innovation.

**Notes:** This section highlights Western University's efforts in supporting research commercialization, industry collaborations, and startup development. It emphasizes turning academic research into marketable innovations.

Overview

Introduction to intellectual property
Types, Focus on patents
Requirements for patentability: novelty, obviousness, utility, and subject-matter eligibility
Anatomy of a patent
Western spin-out example
Various stages in the lifecycle of a patent: drafting, prosecution, enforcement

**Notes:** Intellectual property (IP) is key to protecting innovations. This overview introduces the different types of IP and the focus on patents, explaining what makes an invention patentable.

IP Rights by Type

Intellectual property refers to creations of the mind with moral and commercial value that are protectable by law. Examples include:

Contracts
Patents
Copyright
Trademarks
Plant varieties
Trade secrets

**Notes:** Intellectual property covers different forms of protection, ranging from patents (which protect inventions) to trade secrets (which protect confidential business information).

Contracts

Examples include:

Non-compete terms (employee)
License of IP rights to a third party (owner)
Anti-reverse engineering terms (licensee)
Assignment of IP rights (employee to employer)

Affordable to gain protection
Protection defined by specifics of the contract
Duration is flexible and defined by the contract
Not limited by statute
Enforcement through contract law

**Notes:** Contracts can be used to protect intellectual property by setting legal restrictions on its use. They offer flexibility in defining terms, unlike patents, which are governed by strict legal rules.

Copyright

Protects the expression of an idea in a tangible medium:
Literary works, motion pictures, music, paintings, computer software, photographs, graphic designs, etc.

Creator granted exclusive rights to the use and distribution of the work
Includes moral rights
Term is for the lifetime of the creator plus 50-70 years

**Notes:** Copyright protects creative works automatically, without requiring registration. However, it does not protect ideas, only their tangible expressions.

Copyright (Continued)

Free and automatic protection
Protection begins as soon as the work is reduced to a tangible medium
Scope of protection is narrow - protects the specific work, not the underlying idea
Creator retains moral rights
Long-term protection that passes to the creator’s heirs automatically
Commercial benefits - supports entire industries (in theory)
Difficult to enforce for individual creators

**Notes:** Copyright protection is strong in theory, but enforcement can be difficult, especially for small creators who lack the resources to take legal action against infringement.

Trademarks

Protects a distinctive design
Identifies the source of goods or services
Can be a word, name, symbol, 3D sign, sound, smell, color, etc.
Used to create brand identity, awareness, and exclusivity

**Notes:** Trademarks help businesses protect their brand identity, ensuring consumers can distinguish their products from competitors.

Trademarks (Continued)

Relatively inexpensive to obtain
Few hundred to a few thousand dollars
Protection lasts while the mark is used in commerce
Mark must identify the source
Use it or lose it

Commercial Benefits:
Brand advantage
Price support

Genericized trademarks can be lost

**Notes:** Trademark rights last indefinitely, but they must be actively used in commerce. If a trademark becomes too commonly used (like "Aspirin" or "Escalator"), it can lose its protection.

Trade Secrets

A trade secret is any information not known outside of an organization that provides a competitive advantage.

Examples include:
Formula for Coca-Cola - decided not to patent
KFC Recipe - no single facility has access to the complete recipe; only select executives have access
Formula for WD-40 - formula mixed in only a few facilities to maintain secrecy

**Notes:** Unlike patents, trade secrets do not expire but require strict secrecy to remain protected. If a competitor discovers a trade secret independently, they can legally use it.

Trade Secrets (Continued)

Low monetary cost to gain protection
Must take diligent precautions to maintain secrecy
Indefinite protection if secrecy is maintained
Relates to ease of reverse engineering

Commercial Benefits:
Barrier to market entry
Monopoly pricing

Enforcement is complicated!

**Notes:** While trade secrets can last forever, they can be lost if improperly handled. Enforcement is difficult since it relies on proving unauthorized disclosure rather than patent infringement.

Patents 101

Form or Function

**Notes:** Patents protect functional innovations rather than artistic expressions (which are covered by copyright).

Utility Patents – A Patent Is?

A patent is a negative right.

The patentee can exclude others from making, using, or selling an invention.
Does not give the right to exploit the invention
An issued patent does not guarantee financial return

**Notes:** Patents do not automatically generate revenue. They only prevent others from using the invention without permission. Commercial success depends on business strategy.

Anatomy of a Patent

Western Spinout: Aufero Medical
Developed a mechatronic device to control movement of a force-sensing catheter
Device actuates the catheter during heart ablation procedures
Actuation ensures consistent contact between the tip and the heart wall
Minimizes the need for repeat procedures

**Notes:** This real-world example shows how a university research project became a commercialized product with patent protection.

Patent Summary

If you meet the standard for patentability, you get the right to exclude others from using the invention.
But, not necessarily an affirmative right to use the invention!

Patenting is always a choice.
Maintaining a trade secret might be an alternative.

Risks of not patenting an invention:
Can secrecy be preserved?
Can invention be reverse engineered?
Can you license or execute a contract without patented IP?

**Notes:** Choosing between patents and trade secrets depends on factors like the likelihood of independent discovery and the ease of reverse engineering.

Patent Summary (Continued)

Patenting is expensive!
Drafting costs, filing fees, prosecution costs, maintenance fees, litigation costs
$25,000-$50,000+ per jurisdiction
Litigation could go into the millions!

Limited term of protection
20 years from the filing date
Only issued patents can be enforced

Pendency in the Patent Office can be long and eats into the patent term
Some applications lose as much as 50% of the patent term during prosecution

Only enforced in the jurisdiction of issue
May need to litigate in multiple countries

Presumption of validity upon issuance, but patents can be challenged in court

**Notes:** Patents require a significant financial investment and strategic planning. They provide strong protection but are costly and time-limited.

IP Summary

How else can Aufero Medical protect their commercial activities?
Trademark - names and distinctive marks
Copyright - software that operates the device
Contracts - employee contracts, in-license, partnerships
Trade secrets - software, data, algorithms

Intellectual property comprises legal tools to protect your business, but it’s important to ensure that the financial investment is sound and serves the business case.