

Lecture #6

IP & legal

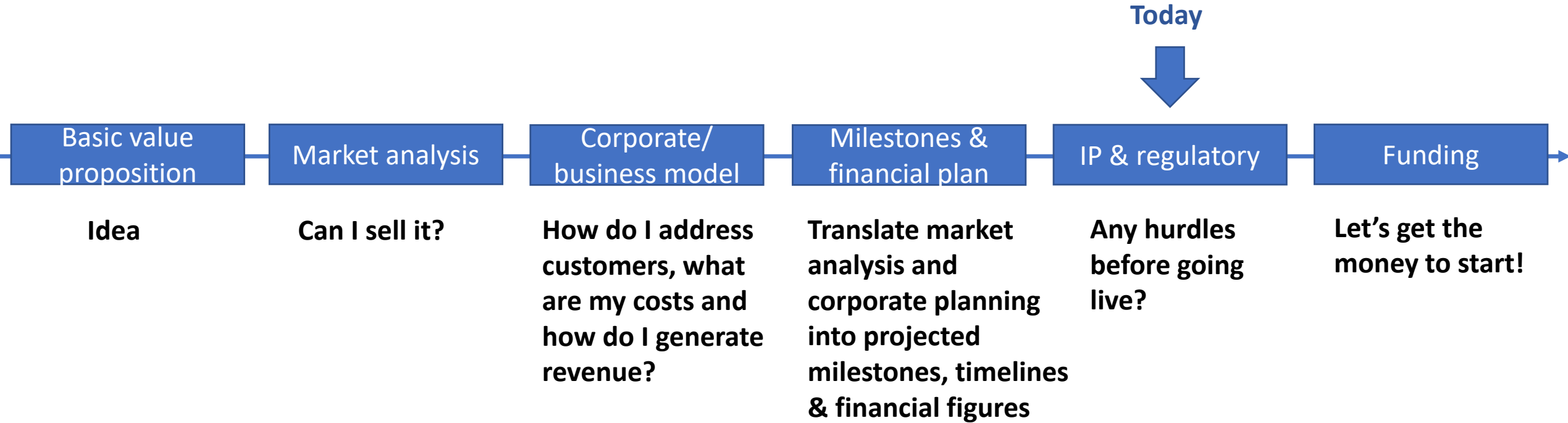
Aims:

- Understand what legal (patent law) and regulatory issues must be addressed BEFORE operating on the market

Course content and schedule 2025

Lecture #/Date	Topic	Details	Seminar tasks
1/ 11.09	General Introduction	Aims of the course, expectations, tasks and assessments General proceeding	Watch Elisabeth Holmes Documentary (Theranos story)
2/ 18.09	Roadmap from academic idea to startup	template business example, Learn about all the steps needed to translate a scientific idea into a startup and what your pitch deck should include => Focus on Value proposition and Business model	Define customer value proposition, USPs and business model (= business example) of Theranos Grouping and assignment of individual presentations
3/ 25.09	Market analysis	Market size, competitors, customer models, growth and scalability,	Introduction into (GlobalData), Find market data on your business example & group innovation
4/ 02.10	Corporate planning	Business models, exit strategies, website & visibility,	Define business example of your group innovation, define markets and competitors
5/ 9.10	Business examples	Business examples 1-4 , detailed feedback	
6/ 16.10	Timelines & initial steps, finance plan	Business examples 5-8 Milestones and finance plan from idea to startup/product	Prepare milestones and financial plan for your startup idea
23.10 – no lecture!			
7/ 30.10	Intellectual property and other legal issues	Business examples 9-12 Patents – facts, data bases, examples Concept of freedom to operate, regulatory hurdles, etc.	Find & analyze patents in your field
8/ 06.11	How to secure funding	Business examples 13-16 Public funding programs, investments, venture capital, EPFL programs	Finalize pitch deck
9/ 13.11	Finalizing the pitch deck	Business examples 17-20 Recap: Detailed analysis of individual case studies, last year's best group pitch and TheraMe pitch	
11/ 20.11	Guest speaker Daniel Alpern (Alithea)	Business examples 21-24 Real-world EPFL startup insight	Prepare Executive Summary and commercial potential in C4Lformat.
12/ 27.11	Guest speaker Luc Henry (Limula)	Real-world EPFL startup insight	
13/ 04.12	Pitches Groups A (e.g. 4-6) Feedback Groups B (e.g. 1-3)	10min pitches with non-presenting students to provide written feedback	Prepare written feedback on other group's pitches
14/ 11.12	Pitches Groups B (e.g. 1-3) Feedback Groups A (e.g. 4-6)	10min pitches with non-presenting students to provide written feedback	
11.12 at 10:15 am	Trophy Award & Feedback		

Timelines and further proceeding of course BIO-490



Patents and legal issues

Commercialization

1. What is the **USP**? Is there a **market** and how big is it?
2. How do I address my **customers**, what is the **business model**, is it **scalable**?
3. What is needed (**time, budget and resources**) to develop a minimal marketable product (**MMP**)?
4. Do I have **patent protection** and **freedom to operate**? Any other **legal or regulatory hurdles**?
5. How to secure **funding**?

Patents – how to file, life time, dependencies

Do I infringe other patents when selling my product or service?

What certifications (e.g. CE, ISO) are required for diagnostic products? Are there ways to circumvent certification in the beginning?



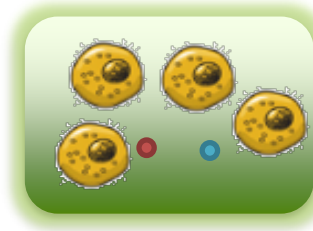
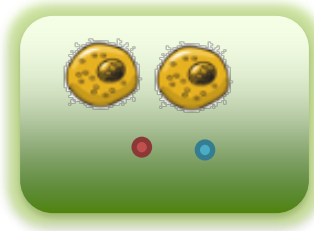
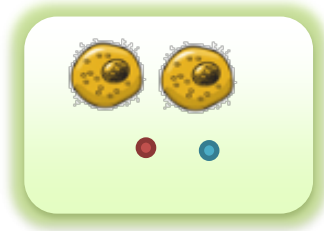
=> today's lecture on patents and legal issues

Patents

- While **scientific papers mainly look back** and describe experiments that have already been performed, the claim set of a **patent tries to prospectively envisage all possible ways of doing the same kind of experiment in the future**. It also tries to cover all possible future applications of the claimed technology.
- The **patent language** is very different from the language used in a scientific publication
- Patent claims are set in a **hierarchical order** to have fall back points in case specific claims are not granted:
 1. We claim the universe
 2. We claim earth
 3. We claim Europe
 4. We claim Switzerland
 5. We claim all Swiss cities starting with L and having more/less than X inhabitants
- The patent must describe something **novel and inventive** to be granted. The described invention **must not be obvious** to a person trained in the art
- **Patent life time is 20 years** in the US, starting from the priority date (submission of first application)
- Patents are **published only 18 months AFTER submission** of the initial patent application (priority date)

A real world example

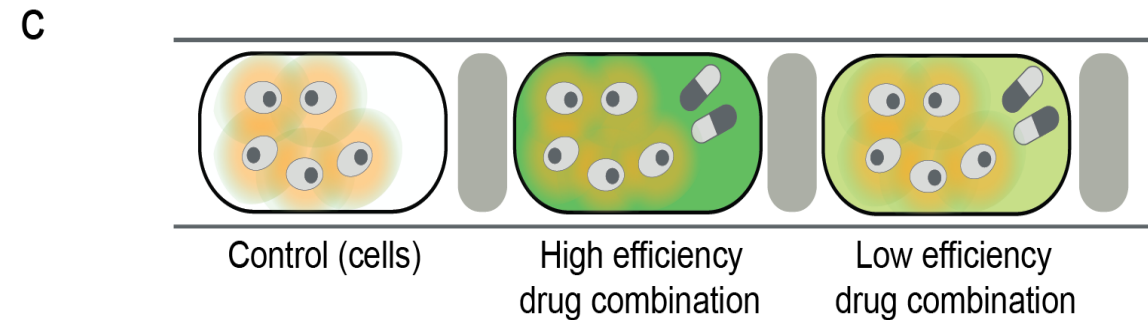
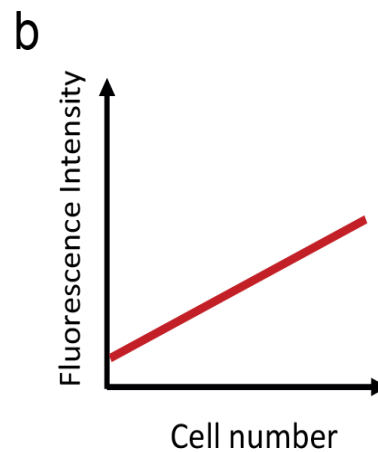
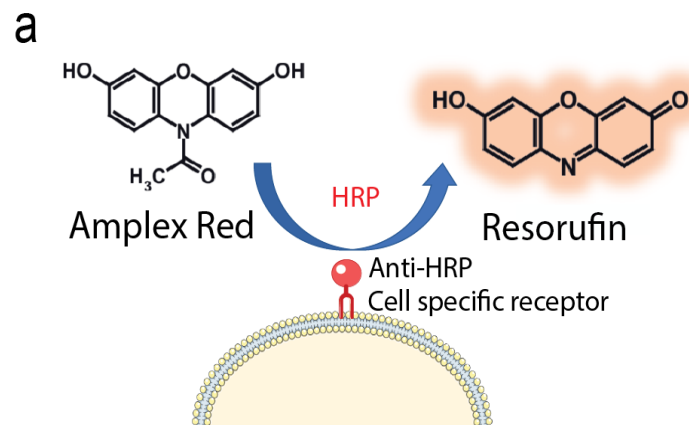
Performing assays in droplets it is not easy to distinguish between a) a strong assay signal because of an unusual high number of cells or b) because of particularly efficient drugs:



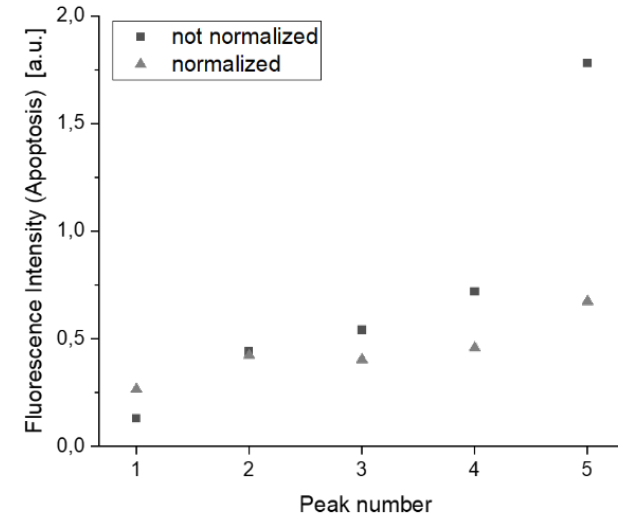
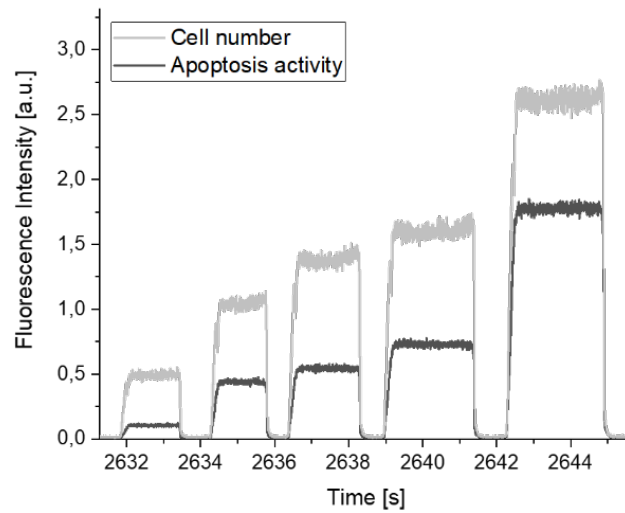
High signal
because of
efficient drug

High signal
because of high
cell number

Solution: Stain cells with antibodies generating a fluorescence signal that correlates with the cell number:



Quantifying the number of cells per droplet and normalizing the apoptosis signal to it



EPFL Patent application EP21170297.2

Corresponding patent application

CLAIMS

1. A method **for the quantification of the number of target entities encapsulated in a micro compartment**, the method comprising the steps of:

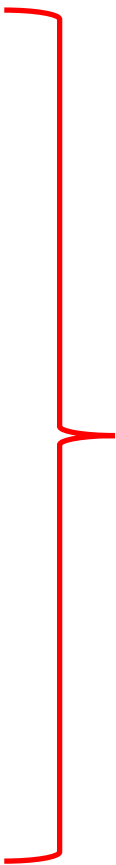
(a) Providing a **detection molecule** comprising (i) a target binding site specific for the target entity, or at least capable of binding to the target entity, and (ii) an **enzymatic component** capable of catalysing a chemical signalling reaction;

(b) **Bringing into contact the detection molecule and the target entity** to allow for a specific binding of the detection molecule to the target entity;

(c) Optionally, removing at least any unbound detection molecules;

(d) **Encapsulating** one or more (**an unknown number of**) **target entities bound with detection molecules** into one or more micro-compartments together with substrate molecules, wherein the substrate molecule is a substrate of the enzymatic component, and which when brought into contact with the enzymatic component renders the enzymatic component to catalyse the chemical signalling reaction; and

(e) **Quantifying the detectable signal for each micro compartment** and thereby quantifying the number of target entities encapsulated in each micro compartment.



Individual steps are NOT novel. Only the combination of these steps creates a unique niche

Corresponding patent application

2. The method of claim 1, which is for the quantification of the number of encapsulated target entities of **distinct species of target entities** out of a plurality of species of target entities, wherein the method comprises the steps of

(a) Providing **multiple species of detection molecules**, each species of detection molecules comprising (i) a target binding site **specific for a distinct species of target entity** out of a plurality of species of target entities, or at least capable of binding to a target entity out of a plurality of species of target entities and (ii) an enzymatic component that is capable of catalysing a chemical signalling reaction catalysed by any other enzymatic molecules;

Same as Claim one but for multiple different target entities in parallel

(b) Bringing into contact the multiple species of detection molecules and the plurality of species of target entities to allow for a specific binding of the detection molecule to the target entities;

(c) Optionally, removing at least any unbound detection molecules;

(d) Encapsulating one or more (an unknown number of) target entities of each species of target entities bound with detection molecules into one or more micro- compartments together with **multiple species of substrate molecules**, wherein each species of substrate molecule is a substrate for the enzymatic component of not more than one species of detection molecule, and which when brought into contact with the corresponding enzymatic component, the enzymatic component catalyses the chemical signalling reaction that generates a distinct detectable signal for each of the chemical signalling reactions;

(e) detecting each detectable signal for each micro compartment and thereby quantifying the number of target entities of each species of target entities encapsulated in each micro compartment.

Corresponding patent application

3. A method for the quantification of the number of target entities encapsulated in a micro compartment, the method comprising the steps of:
- (a) Providing a **first detection molecule** comprising (i) a target binding site specific for the target entity and (ii) a **binding site capable of being bound by a second detection molecule**;
 - (b) Providing a **second detection molecule** comprising (x) a **target binding site specific for the first detection molecule**, and (y) an **enzymatic component capable of catalyzing a chemical signaling reaction**;
 - (c) Bringing into contact the first- and the second detection molecule and the target entity to allow for a specific binding of the first detection molecule to the target entity and a specific binding of the second detection molecule to the first detection molecule;
 - (d) Optionally, removing at least any unbound detection molecules;
 - (e) Encapsulating one or more (an unknown number of) target entities bound with first and/or second detection molecules into one or more **Indirect detection via 2ndary antibody** molecules, wherein the substrate molecule is a substrate of the enzymatic component, and which when brought into contact with the enzymatic component renders the enzymatic component to catalyse the chemical signalling reaction; and
 - (f) Quantifying the detectable signal for each micro compartment and thereby quantifying the number of target entities encapsulated in each micro compartment.

Corresponding patent application

4. The method of **any one of claims 1 to 5**, wherein the target entity is a **particle, such as a micro or nano particle, a bead, a vesicle, a biological cell, or a cell-accumulation, such as a tissue fragment, spheroid or organism**, in particular an embryo or microscopic multicellular organism (worm, plant, fungus, etc.).

5. The method of **any one of claims 1 to 4**, wherein the enzymatic reaction is a **colorimetric, chemiluminescent or fluorescent reaction**.

6. The method of **any one of claims 1 to 4**, wherein the target entity is an **aqueous micro compartment such as a vesicle, a bead, a vesicle, a biological cell, or a cell-accumulation, such as a tissue fragment, spheroid or organism**.

7. The method of **any one of claims 1 to 4**, wherein the target entity is **encapsulated within each micro compartment in excess of the concentration of the detection molecule in the same micro compartment**.

8. The method of **any one of claims 1 to 7**, wherein each target entity when encapsulated is capable of eliciting one or more detectable assay signals, and wherein the method comprises in step (e) **detecting the detectable assay signal, and normalizing the detectable assay signals of two more micro compartments with the detectable signals** for each of the two or more micro compartments

Providing many more details for the previous claims as fall back points (instead of claiming the universe we now only go for specific countries)

Corresponding patent application

9. A plurality of micro compartments, of which at least 5% of micro compartments have an aqueous phase comprising a target entity bound with detection molecules, wherein the detection molecule comprises (i) a target binding site specific for the target entity and (ii) an enzymatic component that is capable of catalysing a chemical signalling reaction; and an unbound substrate molecule dissolved within the aqueous phase and which is a substrate of the enzymatic component of the detection molecule, and which when brought into contact with the enzymatic component renders the enzymatic component to catalyse the chemical signalling reaction that generates a detectable signal.

10. The plurality of micro compartments of claim 9, wherein the target entity is a particle, such as a micro or nano particle, a bead, a vesicle, a biological cell, or a cell-accumulation, such as a tissue fragment, spheroid or organism, in particular an embryo or microscopic multicellular organism (worm, plant, fungus, etc.).

Claiming a product rather than the method to generate it

Corresponding patent application

- 11.** The plurality of micro compartments **of claim 9 or 10**, wherein the enzymatic reaction is a **colorimetric, chemiluminescent or fluorescent** reaction.
- 12.** The plurality of micro compartments **of any one of claims 9 to 11**, wherein the enzymatic component or enzyme is a **peroxidase, or a fragment thereof, or a luciferase** or a fragment.
- 13.** The plurality of micro compartments of **any one of claims 9 to 12**, wherein the substrate **molecule is encapsulated within each micro compartment** in excess to the concentration of the detection molecule in the same micro compartment.
- 14.** The plurality of micro compartments of **any one of claims 14 to 22**, wherein the micro compartment is an aqueous micro compartment such as a **plug, a (microfluidic) droplet or a well**.
- 15.** The plurality of micro compartments **of claim 14**, wherein the micro compartment is a **plug formed in a three-phase system** preferably composed of an aqueous phase, a fluorinated oil phase as a carrier phase, and a mineral oil phase as a spacer between individual plugs of the plurality of micro compartment.

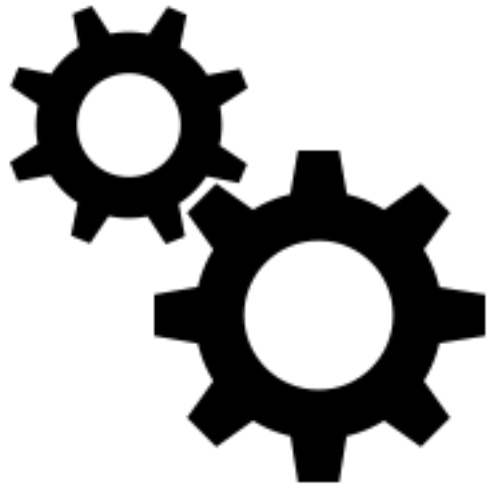
Providing even more details for the previous claims as fall back points (instead of claiming the countries we now only go for specific cities)

Excercise: Now that you got the general concept, let's draft a patent protecting the wheel!



What could be a good claim set?

Did you also include this?



Freedom to operate (FTO) – what external IP do I need for my product or service?

If your invention or service requires additional background IP (e.g. if your invention builds upon previous technological developments by others) one has to be very careful!

Possible solutions:

- ⇒ Background IP has reached end of patent life time
- ⇒ Background IP is not protected in particular countries
- ⇒ Background IP can be licensed, either exclusively (expensive, unlikely to be available), for particular applications (only focus of startup) or non-exclusively

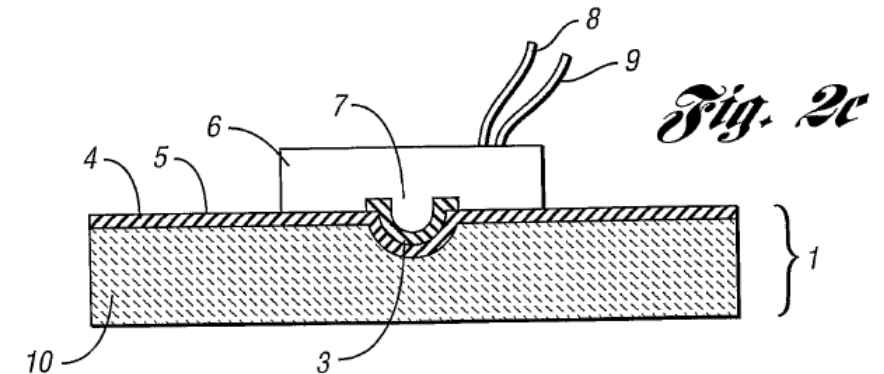
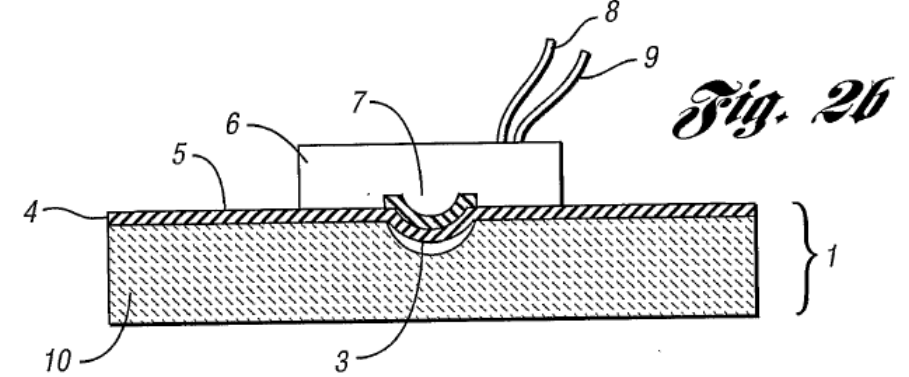
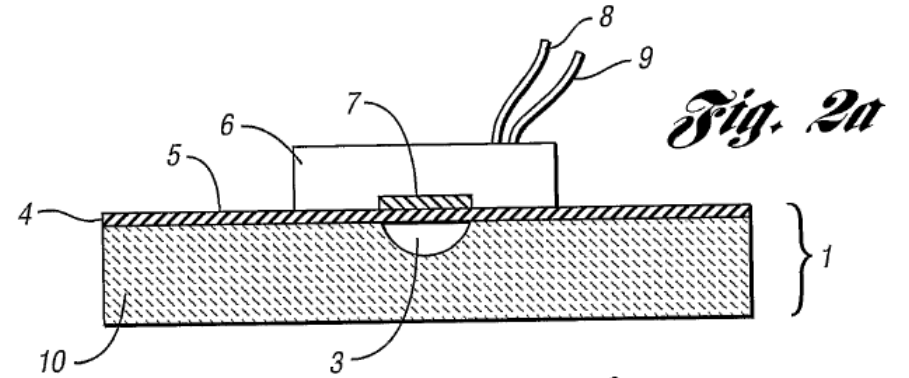
Let's first identify what patents might interfere with the technology developed by TheraMe!, and how patent dependencies look like:

Patent dependencies

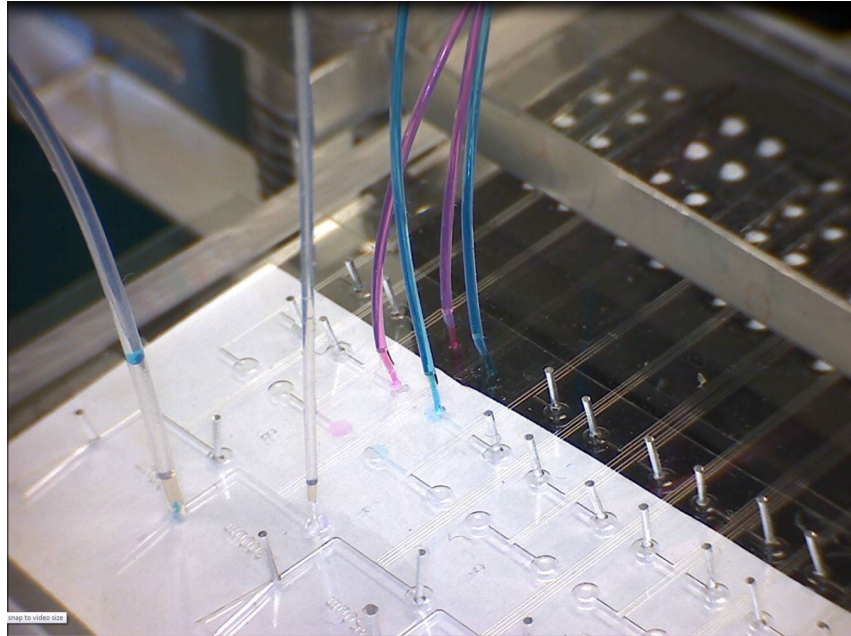
WO2004081741A2, priority date = 2003-03-10

1. A microfluidics device comprising a substrate having therein at least one **empty space whose shape and/or volume is desired to be altered**, said empty space defined on one side thereof by a **deformable elastomer layer**; and an electronically addressable tactile actuator proximate a side of said elastomer layer remote from said empty space, said tactile actuator having a plurality of spaced apart individually addressable extendable protrusions, at least one of which, when actuated, bears upon said deformable elastomer layer, deforming said layer, and altering the shape and/ or volume of said empty space.

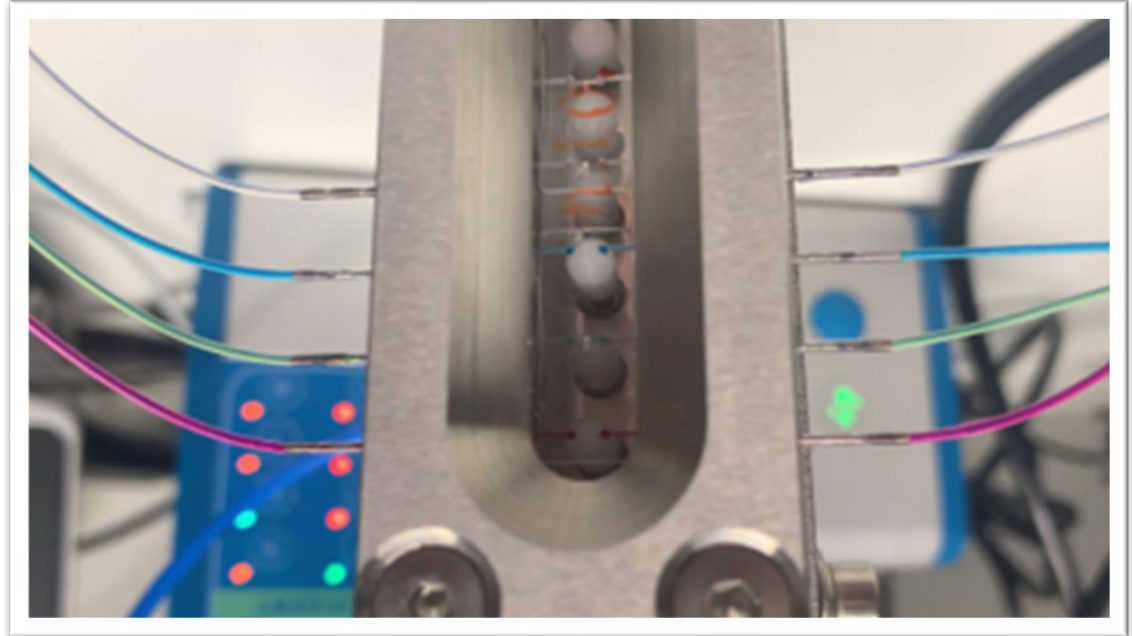
Initial Japanese Braille patent (no mixing, no droplets), only covers the use of deformable elastomers. Furthermore it already expired in 2023!



Patent dependencies



Patent protected until 09.03.2023 (in the US, not necessarily worldwide).



NOT covered by WO2004081741A2

Patent dependencies

US20140332083A1, priority date 2011-09-14

A **microfluidic apparatus** (2) for providing one or more substance liquids to a microfluidic channel network (30), the microfluidic apparatus (2) comprising at least one first substance liquid inlet (401, 405, 411, 415, 421, 425, 431, 435, 441, 445), at least one first valve (412) and at least one input device for continuously applying a substantially constant pressure or a substantially continuous flow to the at least one first substance liquid at the at least one first substance liquid inlet (401, 405, 411, 415, 421, 425, 431, 435, 441, 445), wherein the at least one first valve (402, 406, 412, 416, 422, 426, 432, 436, 442, 446) is **switchable between a first position in which a liquid connection to the microfluidic channel network (30) is open and a second position in which the liquid connection to the microfluidic channel network (30) is closed.**

2. (...)

3. The microfluidic apparatus according to claim 1, further comprising: a separation liquid channel; and a **droplet channel;**

wherein the separation liquid channel is connected to the droplet channel at a droplet generation junction and the droplet generation junction is connected to the microfluidic channel network.

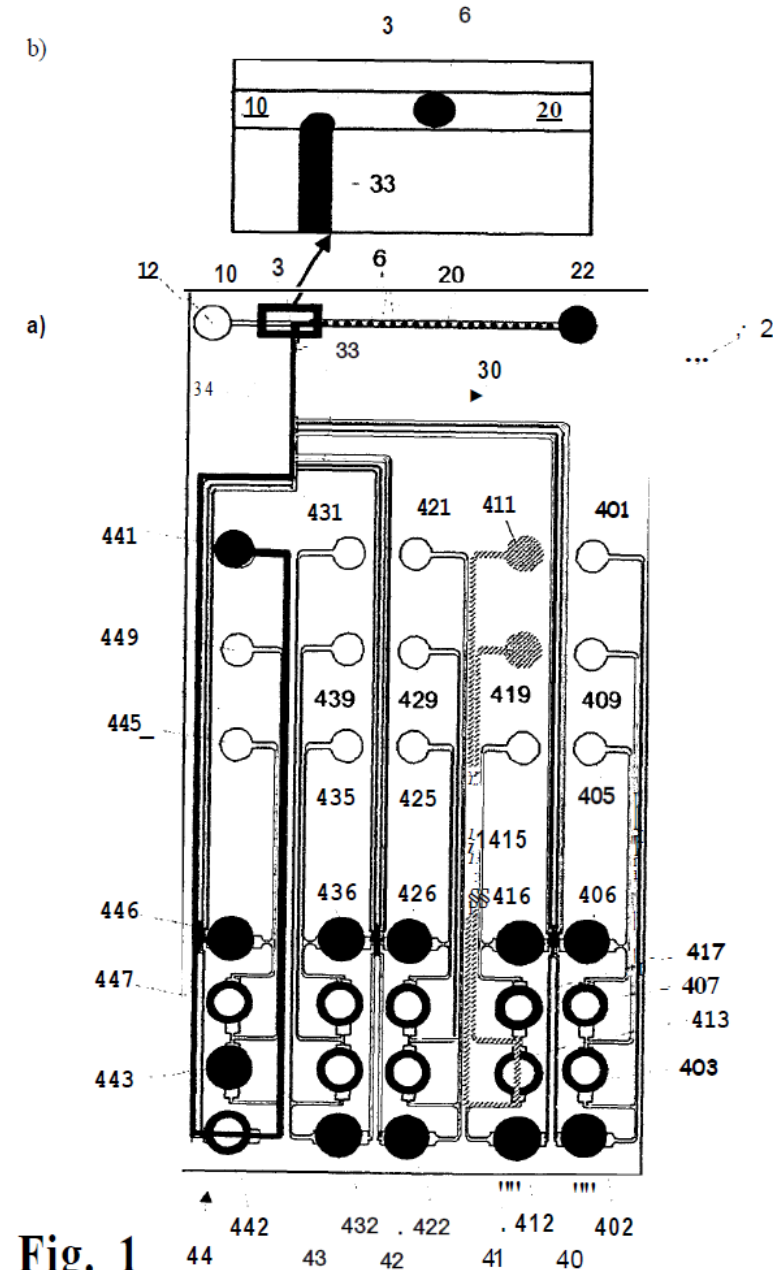


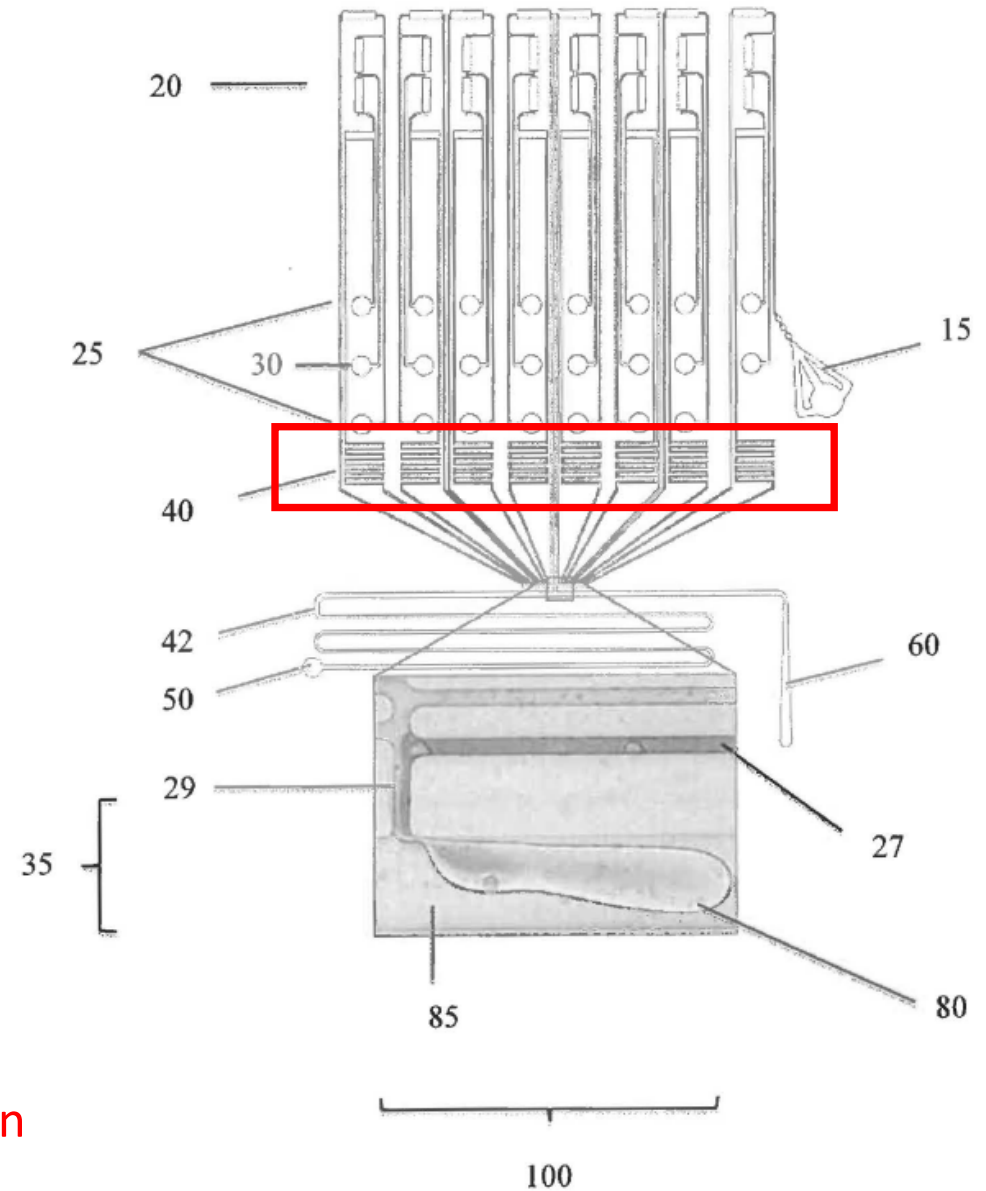
Fig. 1

Dependent on WO2004081741A2 until 2023-03-09 if using elastomeric polymer as substrate for microfluidic chips

Patent dependencies

EP14186463, priority date 2014-09-25

I. A microfluidic device for producing droplets of at least one sample into an immiscible phase, the device comprising a droplet maker connecting an immiscible phase channel and a sample channel having at least one sample inlet connected to at least one sample inlet channel injecting the at least one sample into the sample channel, wherein the injection of the at least one sample is controlled by at least one sample valve, so that the at least one sample flows either towards a sample waste outlet or into the at least one sample inlet channel, wherein different sample inlet channels of the at least one sample inlet channel have the same hydrodynamic resistance resulting from the length, height and width of each sample inlet channel upstream of the droplet maker.



Dependent on WO2004081741A2 until 2023-03-09 and on US20140332083A1 until 2031-09-13

Patent dependencies

US20180355407A1, priority date 2015-06-26

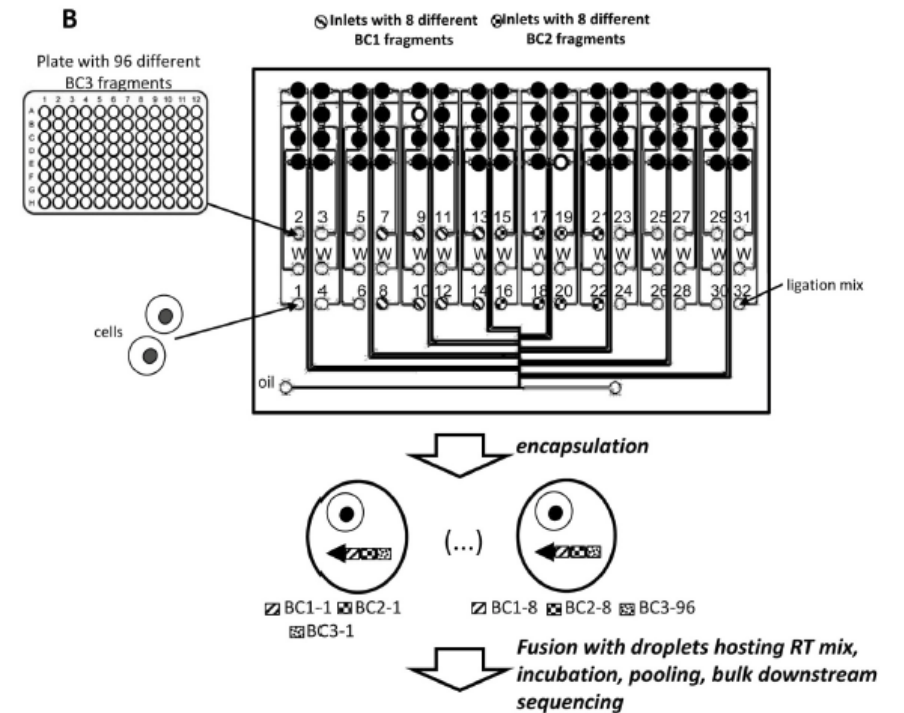
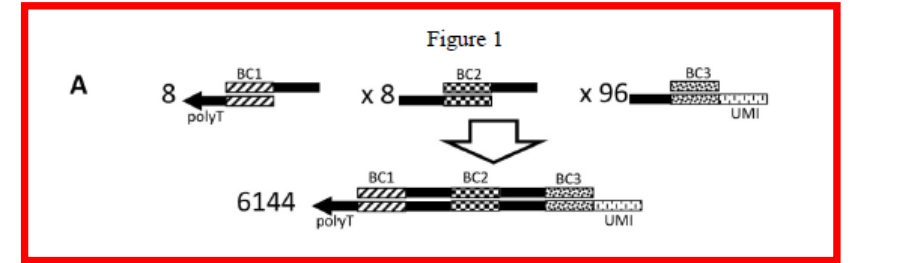
1. A method for co-localizing a particle comprising DNA and/or RNA with a known barcode oligonucleotide or set of components thereof in a microfluidic droplet in a microfluidics system, comprising:

- (i) feeding a particle comprising DNA and/or RNA into a co-localizing channel,
- (ii) passing the particle past a series of at least two valve-operated oligonucleotide inlets or sets of valve-operated oligonucleotide inlets, wherein one of the at least two oligonucleotide inlets or sets of oligonucleotide inlets is open while the particle passes it, and wherein each 10 oligonucleotide inlet, when open, feeds a known barcode oligonucleotide or set of components thereof into the co-localizing channel, or each set of oligonucleotide inlets, when open, feeds a set of components of a known barcode oligonucleotide into the colocalizing channel, and
- (iii) closing the oligonucleotide inlet or set of oligonucleotide inlets that is open after the 15 particle has passed it and opening a different oligonucleotide inlet or set of oligonucleotide inlets of the at least two valve-operated oligonucleotide inlets or sets of valve-operated oligonucleotide inlets, wherein

(A) the particle of step (i) and the known barcode oligonucleotide or the set of components 20 thereof of step (ii) are fed into the co-localizing channel while not comprised in microfluidic droplets, and the method further comprises generating microfluidic droplets downstream of the at least two valve-operated oligonucleotide inlets or sets of oligonucleotide inlets prior, during or after step (iii), including a microfluidic droplet comprising the particle and the known barcode oligonucleotide or components thereof, or

25 (B) the particle of step (i) and the known barcode oligonucleotide or the set of components thereof of step (ii) are fed into the co-localizing channel comprised in microfluidic droplets and these microfluidic droplets are fused.

Bio application, NOT device geometries!



BC1-1-BC2-1-BC3-1AATGGCCA...	global RNAseq for sample
BC1-1-BC2-1-BC3-1GGTACCAA...	BC1-1-BC2-1-BC3-1
BC1-8-BC2-8-BC3-96TCTAAGCC...	global RNAseq for sample
BC1-8-BC2-8-BC3-96CCTGAATC...	BC1-8-BC2-8-BC3-96

Dependent on WO2004081741A2 until 2023-03-09 and on US20140332083A1 until 2031-09-13 and on EP14186463 until 2034-09-24

How and where to find patents that possibly interfere with the commercialization of your idea?

US patent and trademark office (www.uspto.gov)

- Very comprehensive, including tutorials
- Nice also for searching trademarks


European Patent Office Search Engine (https://worldwide.espacenet.com/?locale=en_EP)

- Easy to use & efficient

Google Patents (www.google.com/patents)

- Often allows complementary searches using real-world search terms (“first droplet sorting patent“, “most important...” – try also directly on google!)

How and where to find patents that possibly interfere with the commercialization of your idea



Europäisches Patentamt
European Patent Office
Office européen des brevets

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|

Application number: ⓘ DE201310112935
|

Priority number: ⓘ WO1995US15925
|

Enter one or more dates or date ranges

Publication date: ⓘ 2014-12-31 or 20141231
|

FTO analysis – to be carried out by a professional law firm

...but: Be aware of at least some relevant patents and check if they show up in their search report

Regulatory issues for IVD

New IVD devices have to be CE certified before market launch AND the startup/manufacturer has to be certified according to ISO 13485 (keep this in mind for all revenue projections).

Details on this can be found on:

<https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation>

<https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices>

A typical certification procedure takes **at least 2-3 years** and requires a clinical performance study!

Regulatory issues for new drugs

Human Clinical Trial Phases (www.centerwatch.com)

Phase I studies assess the safety of a drug or device. This initial phase of testing, which can take several months to complete, usually includes a small number of healthy volunteers (20 to 100) who are generally paid for participating in the study. The study is designed to determine the effects of the drug or device on humans including how it is absorbed, metabolized, and excreted. This phase also investigates the side effects that occur as dosage levels are increased. About 70% of experimental drugs pass this phase of testing.

Phase II studies test the efficacy of a drug or device. This second phase of testing can last from several months to two years, and involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded", which means that neither the patients nor the researchers know who has received the experimental drug. This allows investigators to provide the pharmaceutical company and the FDA with comparative information about the relative safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both Phase I and Phase II studies.

Phase III studies involve randomized and blind testing in several hundred to several thousand patients. This large-scale testing, which can last several years, provides the pharmaceutical company and the FDA with a more thorough understanding of the effectiveness of the drug or device, the benefits and the range of possible adverse reactions. 70% to 90% of drugs that enter Phase III studies successfully complete this phase of testing. Once Phase III is complete, a pharmaceutical company can request FDA approval for marketing the drug

Regulatory issues for new drugs

Clinical trials for drugs = only affordable for IND or phase 1, plan maximally up to this stage and then partner with big pharma:

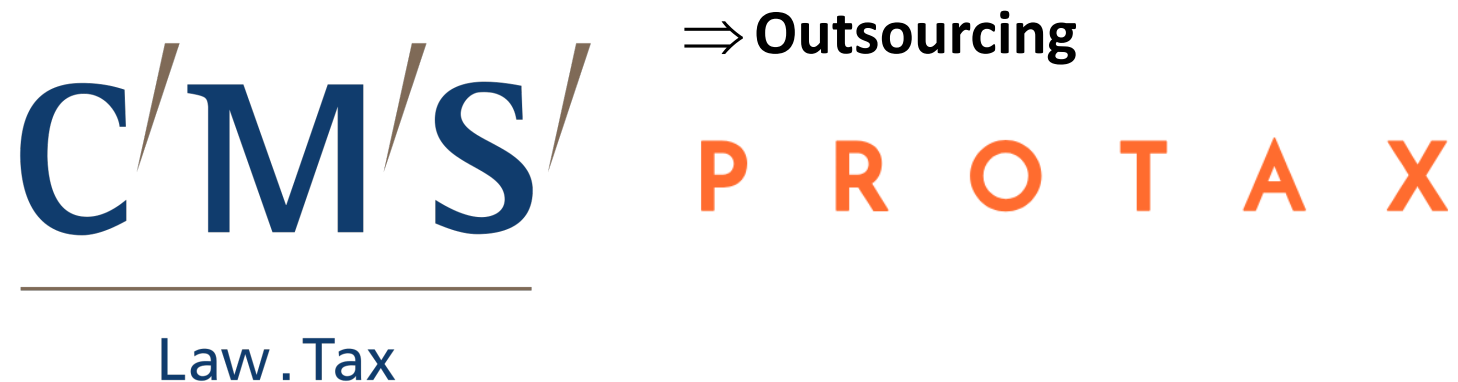
“The average cost of phase 1, 2, and 3 clinical trials across therapeutic areas is around \$4, 13, and 20 million respectively. Pivotal (phase 3) studies for new drugs approved by the Food and Drug Administration (FDA) of the United States cost a median of \$41,117 per patient.”
(<https://www.sofpromed.com/how-much-does-a-clinical-trial-cost/>)”

IND studies are required for getting approval as an Investigational New Drug enabling first in human clinical trials. These studies typically include determination of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMEtox studies) and cost about \$2-3M US\$

Regulatory issues – what other permissions and certifications are needed, e.g. for diagnostic products, drugs or „in human“ applications?



For legal, regulatory or technical issues that you are not trult familiar with...



Spend you time on the things that you are best or which other’s (externals) can’t do. Startups have very limited ressources and tough time lines!

(note that the names and logos of all CROs mentioned in this course should be considered as examples only, they are in no ways meant as any kind of recommendation or quality assessment!)

BIO-490 students tasks for today/ this week

- Perform a patent search in the field of your case study and identify dependencies on third party IP

Potentially threatening patents

- Miller et al., US2021XXYY
- Snyder et al WO2015XXYY

Annotate and summarize the patents you have identified!

- Identify possible regulatory hurdles and solutions and prepare a road map to address them

Questions?

