Putting INVITROM in the market

An advice on the opportunities for INVITROM for funding, membership and content.

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Preface

As the author of this report, I would like to thank quite a few people who played an important part in writing this report.

First and foremost, I would like to thank my internship supervisor, Peter Olinga, for giving me this assignment and helping me think of ways to help INVITROM improve as an organization. Our many meetings on Tuesday afternoon were both inspiring and fun, and I can honestly say that I've enjoyed my time here a lot.

Furthermore, I would like to thank my science, business and policy supervisor, Gert Jan Euverink, for the support he gave me during this internship. Your guidance during the preparatory weeks and the midterm week helped me find the right directions for this report, and your comments where always of great value for my work.

Of course I would also like to thank the board of INVITROM for allowing me to get an inside look on their organization and having me join many of their board meetings. I enjoyed your symposium this year and definitely intend to join you again next year.

I would also like to thank my scientific supervisor, Prof. Dr. Barbro Melgert, for finding the time to help preserve the scientific quality in this report.

Last but not least, I would like some of my colleagues at the UMCG, where I was able to do all my work at Peter Olinga's research group. The coffee breaks and talks in the hallways were always enjoyable and offered me some new insights. Specifically, I would like to thank 3 people who I shared a room with for most of my time here. Sofie, Pieter-Jan and Pascal, we've had more lunch together than I can count, spent time helping each other with our projects and overall you've helped me stay motivated and played an important part in the very pleasant working environment I enjoyed during my internship.

I hope you enjoy reading my work.

Executive summary

For years, the use of animal models has been an important paradigm in biomedical research. These experimental models are based on the concept that every animal, including humans, have a common ancestor. Because of that, they can share similar metabolic and developmental pathways as well as genetic material. Recent reports however, show that animal models are much worse predictors of human biological processes than previously thought. In conjunction with the ethical objections of animal experimentation, an alternative is needed. *In vitro* models provide such an alternative. The field of *in vitro* models has been rapidly increasing over the last decades. With the rise of stem cell inducing techniques, more and more complex and specific models are being generated, both easier and cheaper than animal models. From organoïds to organ-on-a-chip models, scientists are finding more and more ways to mimic the human *in vivo* situation *in vitro* more accurately. The *in vitro* toolbox keeps expanding.

INVITROM is the international society for *in vitro* models. Their mission is the promotion of development, application and acceptance of *in vitro* models. INVITROM believes the best way to stimulate the use of *in vitro* methods is by informing those who work in the many disciplinary fields of biomedical sciences about their potential, as well as stimulating interaction and collaboration between these scientists and society, in the form of businesses and regulatory officers. In order to work towards these goals, they organize an annual symposium. Here, rather than focusing on one specific disciplinary field, INVITROM offers a stage for a wide variety of fields, in hopes of those fields inspiring each other.

INVITROM is a small organization operating in a very large market. However, the direct nature of the market is not very competitive, because most organizations are non-governmental organizations and people attending other events contributes to their own missions as well. This offers INVITROM an opportunity to compete for attendees. Although there are many looking for speakers, the Netherlands and Belgium offer a wide variety of good scientists that could speak at INVITROM's symposia.

The promotional material INVITROM developed this year could have reached an even bigger audience had the program and therefore the promotional material been finished sooner. Ultimately, INVITROM should aim to have the program finalized at least 3 months before the event, which will allow them to present their program effectively to their members and potential sponsors. To make sure this will happen properly, INVITROM should assign a board member to be responsible for generating these materials, which could include certain parts of the website as well.

INVITROM has a great opportunity to have sponsors at their event. Because of the size of their organization they can give sponsors certain offers that bigger organizations are more hesitant towards, which can potentially make them an attractive option. But sponsors should most importantly by sought within the network of the board, as there is already a connection there and probably a shared interest as well, which makes it easier to find a good fit for sponsorship. Furthermore the entire board should have sponsorship in mind when talking to business partners, as opposed to having one person in charge.

Table of contents

I. Introduction

A paradigm in biomedical research

For years, the use of animal models has been an important paradigm in biomedical research. These experimental models are based on the concept that every animal, including humans, have a common ancestor. Because of that, they can share similar metabolic and developmental pathways as well as genetic material. Animal models are then used to investigate these processes where experimentation on humans would be considered unethical. However, the use of animal models has long been a topic of debate. In Europe, the European Union has set up guidelines regarding the use of animals in biomedical research. (CCD 2014) In the Netherlands however, rules and regulations are even stricter than those guidelines. (Rijksoverheid 1977) Furthermore, the Netherlands aim to become leader in animal-free innovation by 2025. (Van Dam, 2017)

The three R's of ethical animal use in scientific research

With the debate surrounding use of animals already ongoing, in 1959 two scientists described three R's of ethical use of animals in research: Reduction, Refinement and Replacement. Reduction encourages the researcher to consider minimizing the number of animals used in their experiments. Refinement is to be considered by the researcher in order to conduct experiments as pain-free and efficient as possible, to minimize the amount animals suffer during experiments. Replacement refers to considering the use of alternatives to animal testing. These can include computer models, non-living tissues and cells, and use of lower-order animals (cold-blooded animals and invertebrates) instead of higher-order animals (Primates and mammals). (Russell & Burch 1959) Animals are used in a high variety of types of research. They are being used to investigate fundamental pathways as well as to model humans in order to elucidate toxic properties of potential drugs and other compounds.

In vitro experiments can provide an alternative

On the other side of the field, *in vitro* models can often offer an alternative. *In vitro* models are the collective name for models using cells, organs or biological molecules outside their normal biological context in biomedical research. With the help of years of scientific developments in the field of *in vitro* models, their potential use keeps expanding. Not only can *in vitro* models nowadays replace certain *in vivo* models, but they can also offer insights on aspects that cannot be investigated *in vivo*. (Polli 2008)

The international organization for *in vitro* methods: INVITROM

INVITROM is the international society for *in vitro* models. They are a learned society of biomedical scientists. They currently have members from the Netherlands and Belgium. They are listed as an association in the Dutch chamber of commerce. (Dutch chamber of commerce 2018) Their statutes are on record. Their mission is the promotion of development, application and acceptance of *in vitro* models. INVITROM believes the best way to stimulate the use of *in vitro* methods is by informing those who work in the many disciplinary fields of biomedical sciences about their potential, as well as stimulating interaction and collaboration between these scientists and society, in the form of businesses and regulatory officers. In order to work towards these goals, they organize an annual symposium. This symposium is their main resource. INVITROM does not have any full-time employees. Everyone involved spends some time next to their jobs at universities or other institutions to run INVITROM. The board currently exists of 5 people, with a chairman, secretary and treasurer. As a part of their board, they used to have a sponsor liaison, in charge of communications with current and new sponsors, but her role has been uncertain during the development of this report.

The aim of this report

This report will discuss ways INVITROM can increase their membership numbers as well as their income, while also discussing the interesting developments in the field of *in vitro* research, which could serve as content for their annual symposium. INVITROM wants to be put in the market. Not only do they want to find their place in their consumer market, which mostly consists of researchers, but also their business market. They would like to investigate what would be the most efficient way to promote them both to sponsors and members. Through this, they can improve their consumer and business market position. Possible organizations that could support INVITROM could be businesses, non-governmental organizations and even governmental organizations. The report will include findings from scientific literature, investigations conducted among INVITROM members, and interviews with experts and organizations within the fields in which INVITROM operates.

Formal framework of this report

This report has been produced in the framework of an educational program at the University of Groningen, the Netherlands, Faculty of Science and Engineering, Science Business and Policy (SBP) Curriculum. The student responsible for this report is a student in Biomedical Sciences, specialized in regenerative medicine. The project was carried out from 08-01-2018 to 01-08-2018. During this time, the student was supervised by the people listed below. (Table 1)

Table 1 - Project supervisors

Name	Institute	Function	Role in supervision
Prof. Dr. P. Olinga	INVITROM	Chairman	Daily supervisor
Prof. Dr. B. N. Melgert	University of Groningen	Teacher	Science supervisor
Prof. Dr. G. J. W. Euverink	University of Groningen, Professional Training 'Science+Business&Policy'	Teacher	SBP Supervisor
G. Prins	INVITROM	Board member	Supervisor

Reading guide

In this report, the interesting scientific developments in the field of *in vitro* research will be discussed first. Second, there will be an internal analysis of INVITROM as an organization, as well as an analysis on the annual symposium. Then marketing will be discussed for the annual symposium, including an external analysis for the competition as well as possible sponsors. Next, funding will be discussed, with current sponsorship practice being analyzed critically. Then the findings will be integrated and form an advice that will consider which steps need to be taken to carry out the advice.

II. Scientific analysis

In this chapter some of the interesting scientific aspects of *in vitro* methods will be discussed. First, the potential of stem cells for both research and medical therapies will be discussed. Then I will elaborate on the emergence of organ-on-a-chip models and some of the challenges that these models still face. I will then continue with assessment of scientific communication and collaborations, as well as discuss the developments on reducing animal experimentation in the Netherlands and Belgium. Furthermore, I will discuss some of the scientific aspects of *in vitro* methods through the field that perhaps stands out most: Toxicology. Finally, genome editing and specifically the rise of the CRISPR-Cas9 system will be discussed.

Stem cell research: An interesting and promising field

Induced Pluripotent Stem Cells (iPSCs) have a lot of potential in biomedical research. Somatic cells such as fibroblasts can be harvested relatively stress free from any human. These can then be reprogrammed using a few transcription factors. (Takahashi et al. 2007) Because of this, testing on cells from patients is a possibility. This will inevitably lead to more and more discoveries being done in not just human-derived, but even patient-derived cells. (Benam et al. 2015) The developments in stem cell generation and culture has opened avenues for investigating diseases that were very hard to study before. These cells also allow scientists to create tissue-like structures, called organoids, which even more closely resemble the *in vivo* situation *in vitro*. Organoids were named method of the year 2017 by Nature publishing group. (Nature publishing group 2018)

A good example of these developments is the study of schizophrenia in neural cells developed from patient-derived cells. (Prytkova & Brennand 2017) Because of our lack of understanding of the human brain, as well as the polygenic character of most mental-illnesses, including schizophrenia, it has been shown to be very challenging to develop predictive *in vivo* models of these diseases. (Nestler & Hyman 2013) Early neuronal *in vitro* models proposed many challenges, as adult matured neurons no longer divide, while immortalized neuronal carcinoma cell lines often significantly differ physiologically from the cell-types from which they were derived. (Gordon et al. 2013) But by using material in which you know the disease genotype exist, in this case patient-derived cells, it is now possible to study these diseases *in vitro*. Although it can still be challenging to determine which molecular defects are causing the diseases, here *in vitro* approaches seem to yield more fruitful efforts than previously possible. (Brennand & Gage 2012) Perhaps the development of the area of stem cells is most exciting for neuronal cell culture. (Gordon et al. 2013)

However, all potential described above does not exempt the use of human iPSCs from any ethical considerations. The use of iPSCs has been associated with the formation of so called embryoid bodies, structures closely resembling embryos. This could put iPSC culture dangerously close to cloning, which is a topic of much ethical debate. (Denker 2012) However, similar structures can be generated using embryonic stem cells and the structures are considered far from recapulating the patterning associated with actual embryos. (Aleckovic & Simón 2008; Denker 2004; Pekkanen-Mattila et al. 2010)

Induced pluripotency takes donor cell age into account

There are some questions raised when looking into how research with iPSCs is being performed. Somatic cells are associated with ageing, while stem cells usually lack many aspects of ageing such as age-associated DNA methylation. Although animals may be a less than sufficient model for human disease, the generation of iPSCs was first reported using mouse cells. (Takahashi & Yamanaka 2006) When looking at studies done with mouse cells however, usually the mouse embryonic fibroblasts (MEFs) are most commonly used for dedifferentiation. This is rather odd, as these cells do not hold cell age into account, but are used to make associations with older human cells being used for similar experiments. Except for when investigating developmental biology, embryonic cells are much less of interest for most research because diseases that develop far beyond developmental stages of life are being investigated. Because the use of embryonic material can be bypassed using iPSC strategies, cells used for both research and cell therapy could be of different ages. This is something that already is considered in other adult stem cell types and one might think they should therefore also be considered when using iPSCs, especially for research. (Diekman & Guilak 2013) Age is associated with accumulation of DNA damage and early cloning experiments showed that this resulted in a decreased lifespan in cloned organisms compared to the donor. However, studies show that typical signs of the ageing process are reversed by iPSC reprogramming and iPSCs from older donors show no significant differentiation potential, early senescence or functional impairments compared to younger donors. (Strässler et al. 2018) It remains to be seen whether these processes also reduce tumorigenicity and epigenetic pattern retention issues associated with ageing. (Strässler et al. 2018; Ravaioli et al. 2018)

Organs-on-a-chip: Building a better *in vitro* model

Another technique that is increasingly being used is the organ-on-a-chip model. This technique uses microfluidics to allow for flow of medium between several compartments on a chip. These compartments can be used to culture all types of cells, even organoids or other *in vitro* models. (Skardal et al. 2017) On these chips, several of the *in vivo* characteristics, such as mechanical stress or exposure to fluid induced shear stress, can be mimicked. (Huh et al. 2010; Kimura et al. 2017) A great example is the organ-on-a-chip model developed by the WYSS institute at Harvard University in Boston. They developed a lung-on-a-chip model that allows for airflow across a layer of alveolar epithelial cells on one side of a membrane, while allowing for blood flow across a layer of capillary cells on the other. The model then allows for stretching of the membrane by using vacuum pressure on side-chambers connected to the membrane. Through all of this, the model can effectively mimic alveolar stretching during breathing *in vitro*. They also investigated whether their model would allow for immune interactions by introducing bacteria in the airflow channel, while adding lymphocytes to the medium flowing through the blood flow channel. Their results show that the lymphocytes are able to penetrate the capillary and epithelial cells in order to encapsulate the presented bacteria. Furthermore, they were able to induce pulmonary edema by introducing IL-2, a cytokine known to cause pulmonary edema, into the blood flow channel. Interestingly, the effect of IL-2 became more apparent when breathing was mimicked by the model, as opposed to when the vacuum channels remained unused. (Figure 1) (Huh et al. 2010)

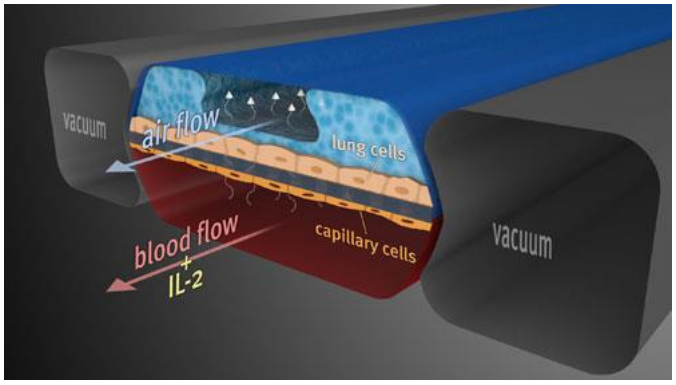

Figure 1- Schematic view of the Wyss Institute's Lung-on-a-chip (Wyss institute website)

Humans-on-a-chip: A step further than the organ

Within the field of these organ-on-a-chip models, researchers are trying to develop methods that would allow for interactions between the several organ-on-a-chip models, usually calling these human-on-a-chip models. The idea is that these models eventually could be designed so that they can truly mimic the *in vivo* situation. There are however still quite some challenges that need to be met. (Caplin et al. 2015) Scaling of the several organ-on-a-chip models should be taken into account. Considering the size of each organ can be done in several ways. Investigators can use allometric scaling, keeping the *in vivo* development and size of each organ in the model in mind. They could opt for histological section scaling, where the designed organ-on-a-chip only has to perform its physiological function, according to the related histological section. The actual size of the model can then be ignored, as the model is considered as a histological section, eliminating some of the complexity of mimicking *in vivo* organs. (Caplin et al. 2015) A third approach may be to scale the models based on organ functions, meaning the preservation of organ function is the most important aspect of scaling. This might oversimplify the design and could decrease translatability of the model. (Caplin et al. 2015) The proposed models would also have to take vasculature into account, as the blood in our bodies is not transported in small tubes, but blood vessels that can have significant effects on the fluids they are transporting. Fortunately, recent studies have shown a possibility to mimic vasculature even in the small microfluidic tubes that are being used in various models. (Hasenberg et al. 2015)

When the organ-on-a-chip models can be expanded into human-on-a-chip models they then allow experiments to take interactions into account between cell types via the circulation of media, mimicking transport by the bloodstream. This contributes to an *in vitro* model that resembles the *in vivo* situation even more closely. This technique seems to be very interesting for toxicological experiments, as it circumvents many of the limitations of other *in vitro* models, as well as limitations of *in vivo* models. Some scientists believe that use of organ-on-a-chip models might be favorable over *in vivo* toxicology assessment, due to its ability to account for interactions between different e.g. organoids, while being a model using human materials. This also takes into account that *in vivo* animal models can have a very low predictability level. (Shanks et al. 2009; Godoy et al. 2013; Marx et al. 2016; Wang et al. 2017) However, it needs to be taken into account that the location specific interactions are still very complex and would be very hard to mimic even in a human- or organ-on-a-chip-model. This would make it unlikely that perfect predictions can be made for the human *in vivo* situation by these models. This does not have to be a very big concern, as they could still outperform most if not all animal models, which as mentioned before have been proven to be ineffective at predicting human *in vivo* outcomes.

The importance of a multidisciplinary view on biomedical research

Traditionally, research has been done mainly within topic boundaries. Biomedical research is almost always sorted by its topic (cardiovascular disease, neurobiology, etc.) and because of this, many discuss their work only with peers within the same subject-based field. This is mainly caused by the increase in complexity of modern day biomedical research. Recently, reports have surfaced discussing the importance of integrating these departments to obtain more successful biomedical research. (Stock & Vacanti 2001; Sharp & Langer 2011) By looking at science from a different perspective, in the case of INVITROM based on the type of experiments used, scientists can familiarize themselves with concepts from other departments, which is believed to be of importance. (Choi & Pak 2006) Not only does transdisciplinary collaboration persist more, but it also produces higher impact papers. (Bu et al. 2018) Ideas from certain subject-based fields have proven to be very useful for other fields. Because *in vitro* research is being conducted within many, if not all subject-

based fields it can quite easily become a platform by which fields can adopt and adapt ideas from each other. In the field of HIV research per example, a technique used to identify rare circulating tumor cells within the field of oncology, now also is being used in the advancement of HIV research by detecting cells able to reproduce HIV particles. (Niessl et al. 2018)

In the current fields of science there is believed to be another challenge for *in vitro* methods. Most scientific journals use the peer-review system to evaluate articles for publication in their journal. It is believed that there is a bias towards publishing studies that use *in vivo* methods over *in vitro* methods. However, when investigating the search results on pubmed and some of the highest ranked (impact factor) journals and publishing groups, there are much more hits using the query *in vitro* over *in vivo*. (Table 2) This points towards more papers being published on *in vitro* studies compared to *in vivo* studies. It must be noted that the ratio between *in vitro* and *in vivo* differs between papers and publishing groups, but even then *in vitro* is found more often than *in vivo*. The higher difference between *in vitro* and *in vivo* using pubmed compared to the rest of the journals and publishing groups could be caused by the fact that there are journals specifically publishing on *in vitro* methods, while most journals publishing *in vivo* research will also publish *in vitro* research. Furthermore, there might still be a difference between *in vitro* and *in vivo* publications in different disciplinary fields. However, when sorting search results, using the filter options of the Web of science search database, based on disciplinary fields there still seems to be a preference for *in vitro* publications. From the 6 biggest fields of research, according to the search engine, in only 1 category (Neuroscience) more publications of *in vivo* compared to *in vitro* biomedical research were found. (Clarivate analytics 2018)

Table 2 - Amount of search results of in vivo and in vitro search queries using several search engines and websites of well-known publishers. (All searches were done on 29-3-18)

Journal/Publishing group	In vivo hits	In vitro hits
Pubmed	799090	1506129
Nature publishing	128132	139145
Nature Journal	15003	19114
New England Journal of Medicine	4347	7312
The lancet	6528	10974
Science publishing	17109	20203
Cell press	23884	38833
BMJ	1447	2910

Personal experience among researchers is still that reviewers are asking them whether they have also investigated their findings *in vivo*, indicating their *in vitro* work alone is not enough to be published. (Appendix I; Personal communications with the INVITROM board) However, based on the search results in many popular search engines and journals, it does not necessarily mean that it makes it more challenging to publish. It might mean the reviewing researcher has an interest for the *in vivo* investigation.

Governmental reports show steady decline in the use of animals in biomedical research in the Netherlands

Data from the 'Zo doende' report of 2016 show that in three categories animals are most used: Applied and translational research, Toxicology and safety testing, and fundamental research. These categories make up over 95% of all animals used for experimentation in the Netherlands. This means that in these categories, most significantly the toxicology and safety testing (35.4%), most ground can be won when it comes to reducing and hopefully one day replacing animal testing. Interestingly, most ground that has been won when comparing 2015 and 2016 was actually on the animals that remained unused, after breeding with discomfort (10.7% vs 0.4%). Overall, use of animals has been decreasing steadily since 2014, with a decrease in among of animal experiments of 15% in 2015 and 2016. (Nederlandse Voedsel- en Warenautoriteit 2014; Nederlandse Voedsel- en Warenautoriteit 2015; Nederlandse Voedsel- en Warenautoriteit 2016)

Reduction of animal use in experimental research is not as successful in Belgium

Data from the Cadenza Document from the Department Living environment, Nature and Energy (LNE) of the Belgian government show that the decline in use of animals in biomedical research has stagnated from 2015 to 2016. (European Union 2015; European Union 2016) Animal use has declined only 5% compared to 14% the year before. Unfortunately, the LNE does not provide data from earlier years, which makes it harder to identify whether this trend is an anomaly or this is a sign that reduction is becoming more challenging in Belgium. It is however very interesting to note that the Belgian reports on animal use in experimental biology is registered for every disciplinary field. This allows to get a better grasp at which fields still use a lot of animals in their research. According to the 2016 report, both in basic and translational research most animals are used investigating the nervous system. (European Union 2014; European Union 2015; European Union 2016)

The importance of *in vitro* models for the future of toxicology

Within the many applications of *in vitro* research, one particular field stands out: Toxicology. Although many aspects below are discussed in the context of hepatology and toxicology, most dilemmas and considerations are also at play in fundamental research in many other disciplinary fields, such as neuroscience or regenerative medicine. There are several reasons that *in vitro* models have become more relevant in the field of toxicology. Although animal testing remains the most important investigative tool for toxicological assessment of new drugs, recent studies have shown that these tests are highly ineffective in predicting the outcome in humans. (Hackam & Redelmeier 2006; McGonigle & Ruggeri 2014; Skardal et al. 2017) The main reason animal testing remains important is the regulatory requirements of animal tests for starting clinical trials in humans. (FDA 2016; ICH Expert Working Group 2002; van den Berg 2016) In recent years there has been an increased desire for implementing the three R's of animal experimentation in biomedical research. (Schechtman 2002; Holmes et al. 2010; Burden et al. 2015) *In vitro* models can hopefully one day replace animal models as an effective means to study drug toxicity.

The main goal of *in vitro* liver models for toxicology is capturing relevant and useful endpoints. Proper study design is key here, as a simple vesicle model can be used to elucidate properties of specific transporters, without closely resembling the *in vivo* environment, while other investigations might need the proposed model to resemble the *in vivo* environment more closely. (Brouwer et al. 2016)Depending on what questions a researcher has, he can have different models at his disposal. These models can range from isolated primary human hepatocytes or hepatic derived cell lines to liver slices and stem-cell derived models, and these models can then be cultured differently to adhere to certain requirements. (Figure 2) (Kyffin et al. 2018)

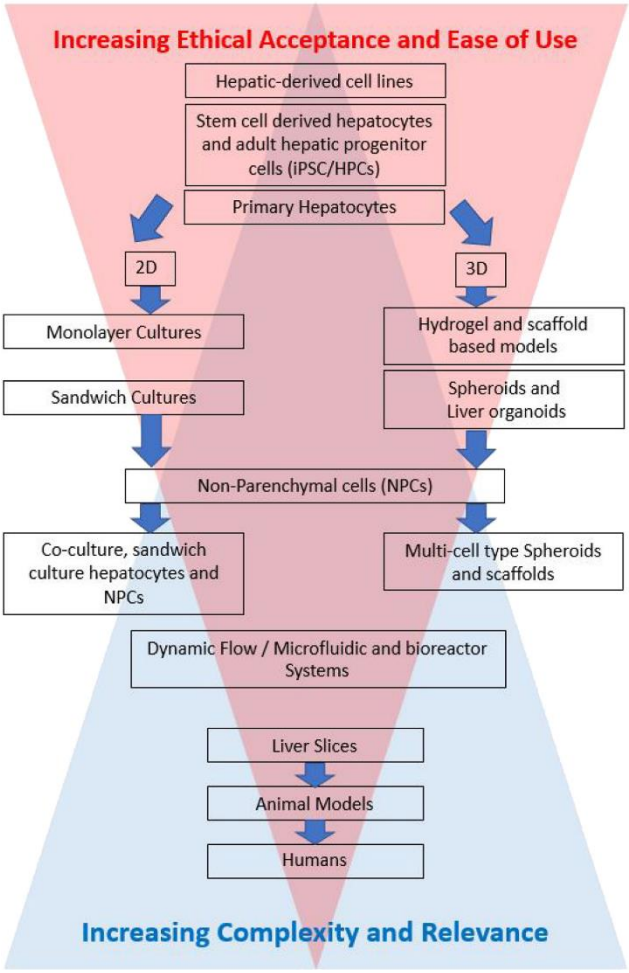

Figure 2 - Increasing ethical acceptance and ease of use versus increasing complexity and relevance of scientifics methods used. (Kyffin et al. 2018)

The best methods currently available

Currently, primary human hepatocytes cultured in a monolayer are regarded as the golden standard of *in vitro* metabolism and toxicity studies. When isolated properly, primary hepatocytes provide a number of preferred activities such as phase I and II metabolic activity, glucose metabolism, urea secretion and albumin production. (Kyffin et al. 2018) Use of these primary hepatocytes however, does not come without its disadvantages. Isolation of primary hepatocytes is quite difficult, they lose their liver-specific function rather quickly, which makes them not suitable for long-term or repeat dose studies, there is a lot of variation between donors and the monolayer culture does not take the complex microenvironment into account that is found *in vivo.* (Bhogal et al. 2011; Godoy et al. 2013; Kyffin et al. 2018) In effort to resolve some of the limitations found in the use of primary hepatocytes, immortalized cells from hepatocellular carcinomas have been used extensively. These cells, such as HepaRG or HepG2, have the benefit that they inherently overcome the limitations of inter-donor variability, phenotype instability and mortality. Also, they are considered to be easily manipulated in the lab. (Donato et al. 2015; Gaskell et al. 2016) Their main drawback is that they often lack expression of key metabolic enzymes. (Gerets et al. 2012)

In efforts to mimic the microenvironment lacking in 2D *in vitro* culture, more and more 3D culture methods are being developed. (Knight & Przyborski 2015) One method uses the microenvironment found *in vivo* exactly. By using precision-cut liver slices (PCLS), researchers are able to maintain the *in vivo* organization of cells and extracellular matrix *in vitro*. This leads to PCLS providing a better comparison to *in vivo* than monolayer culture of primary hepatocytes, where many of the supporting structures and cells are lost in the isolation process. (Elferink et al. 2011) The preparation of liver slices has been standardized for many species, making inter-species studies much easier than many other *in vitro* approaches. (Lerche-Langrand & Toutain 2000) PCLS however still has some of the other drawbacks of primary hepatocyte culture. PCLS are also susceptible to inter-donor variations, as many donors have different underlying conditions. The biggest drawback however is also longevity, as repeat-dose studies cannot be performed with this model beyond three days, as tissue remodeling and formation of new cell lining can be found around the slices after 3-4 days of incubation. (Starokozhko et al. 2015)

The rise of genome editing

Although some of the methods above describe ways in which patient material can be used for research, sometimes this is not an option, due to a variety of factors. Most diseases have underlying genetic defects that completely cause or eventually help develop the disease phenotype. (Renkema et al. 2014; Doudna & Charpentier 2014; Sun et al. 2017; Verma & Sharma 2018; Nestor et al. 2018) By genome sequencing and other screening methods, scientists have been able to identify genetic defects for years. They could then use several methods to try to introduce these genetic defects into their *in vitro* cell lines, which could help them elucidate the mechanisms by which the disease phenotype develops, and subsequently develop therapies to prevent this. Early strategies used the principle of site-specific recognition of DNA sequences by small molecules, oligonucleotides or self-splicing introns. Later zinc finger nucleases (ZNFs) and TAL effector nucleases (TALENs) were used to modify the genome based on the principles of DNA-protein recognition. Most of these methods however where not specific enough and were often quite challenging to perform in the lab. (Doudna & Charpentier 2014)

A major breakthrough in genome editing

In 2012 it was discovered that the genome of basically any cell of any organism could be manipulated much more easily. Earlier, scientists had found that some bacteria and archaea had a working defense mechanism against viral invasion in the host DNA, using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) to detect viral DNA and to remove this DNA by recruiting effector proteins/complexes. (Makarova 2002; Guy et al. 2004) The CRISPR-Cas system has 2 different classes and 5 different types that use distinct mechanisms to find and remove foreign DNA. Class 1 is made up of type 1, 3 and 4 systems, while class 2 contains type 2 and 5 systems. Although there is still not much known about the type 4 subtypes, types 1 and 3 use a complex made up of a wide variety of proteins for targeting this DNA, while the type 2 and type 5 system require only 1 protein for their functionality: Cas9 and Cfp1. This makes the class 2 system very attractive for genome editing. (Lander 2016)

Table 3 - The several classes and systems of the CRISPR system. (Adapted from Lander 2016)

Class	Type	Subtype	Hallmarks	Example effector	Example organism
Class 1	Type I		multisubunit effector complex; Cas3	Cascade	*E. coli*
	Type III	III-A	multisubunit effector complex; Csm effector module; DNA targeting	Cas10-Csm	*S. epidermidis*
		III-B	multisubunit effector complex; Cmr effector module; RNA targeting	Cmr	*P. furiosus*
	Type IV		multisubunit effector complex	DinG family Helicase or small subunit	
Class 2	Type II		single protein effector; tracrRNA	Cas9	*S. thermophilus* *S. pyogenes*
	Type V		single protein effector; single-RNA guided	Cpf1	*F. novicida*

Using CRISPR-Cas9 to specifically target genes of interest for editing

As mentioned above, specificity was a big challenge in genome editing before the rise of the CRISPR-Cas9 system. CRISPR-Cas9 is very specific because it relies on a 20 nucleotide sequence to guide it towards the cleavage site. Naturally, CRISPR-Cas-9 uses the trans-activating CRISPR-RNA (tracrRNA): CRISPR-RNA (crRNA) duplex and a short protospacer adjacent motif (PAM) to direct DNA cleavage. (Doudna & Charpentier 2014) PAM motifs are generally described as '5'-NGG-3'', indicating a sequence with any nucleotide followed by two guanine nucleotides can be a PAM. (Anders et al. 2014) Recent studies however, show that much more sequences can be PAMs for CRISPR-Cas9, increasing the possible cleavage sites present in any gene. (Zhang et al. 2014) The duplex can easily be engineered and fused, creating a single guide RNA (sgRNA), which can be designed specific to the gene of interest. (Zhang et al. 2014) Because the naturally occurring guide can be synthetically generated, the complex essentially forms a 2 component system that can cleave any gene as long as there is a PAM motif adjacent. (Doudna & Charpentier 2014)

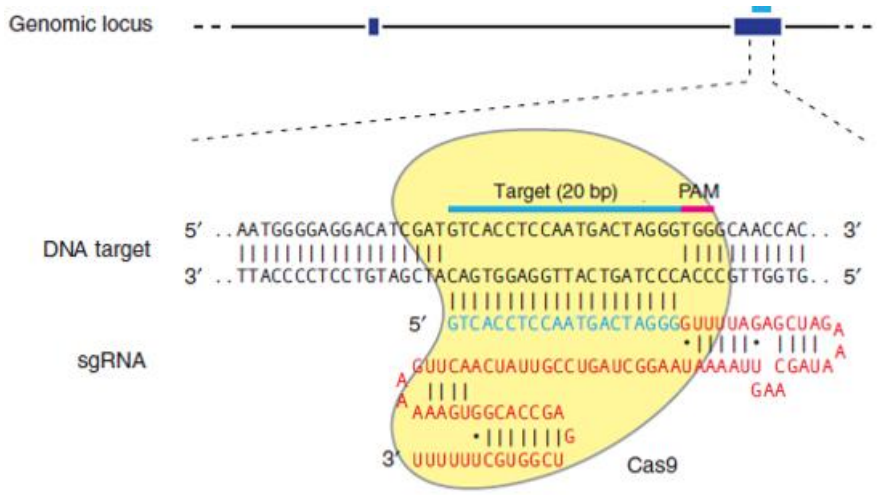

Figure 3 - Schematic overview of the CRISPR-Cas9 system. (Ran et al., 2013)

In vivo versus *in vitro*: a direct comparison

Unfortunately, there is not a lot of work done in the scientific community to directly compare the results of both *in vitro* and *in vivo* studies. This can partially be attributed to a lack of interest: Most scientists want to investigate new and exciting questions and comparing two types of studies often come with the downside of discovering less new information about these questions. Furthermore, most animal testing requires explanation of why the study cannot be performed *in vitro*, or any other alternative, as part of the ethical assessment and approval of the experiments. (United States Department of Agriculture 1999; European Union 2010) This means that not only not many scientists are directly interested in comparison, but also that setting up such an experiment could be very challenging due to legislation. Studies that do make somewhat of a comparison usually describe when each model should be preferred. For bioequivalence studies for example, studies show that *in vitro* studies reduce costs and more directly assess drug product performance for class I and III drugs, as well as highly variable drugs. (Polli 2008)

Concluding remarks

As discussed above, *in vitro* methods have not only good, but very wide potential in biomedical research. From stem cells, both for fundamental research and potential therapies, to organ-on-a-chip models and the many aspects of toxicology research, there seems to be a technique using *in vitro* methods to assess most scientific questions. The Belgian and Dutch governments seem to approve of these techniques as they keep tabs on the reduction of animal experiments. Regulatory bodies will undoubtedly also approve more techniques, as they are already approving some therapies in the European Union. Furthermore, because of the rapid developments in genome editing, possibilities of mimicking the *in vivo* situation using *in vitro* methods are increasing every year. This is supported by the drop in animal research in both the Netherlands and Belgium, even though it seems as though this decrease could be even better, especially in Belgium.

III. Business analysis

In this chapter I will discuss INVITROM as an organization, as well as the market it operates within. I will start with not only analyzing the organization itself, but also the annual symposium they organize. Then I will elaborate on the marketing strategies and tools INVITROM uses and could potentially use in the future. Next I will look into several aspects of the markets INVITROM operates in, which includes the scientific events market and the biotech industry. I will continue by discussing the needs and suggestions by INVITROM members and previous sponsors. Finally I will discuss funding, with sponsorship being discussed extensively.

Internal analysis

McKinsey's 7s model: Analyzing INVITROM as an organization

Below INVITROM will be analyzed using McKinsey's 7s model. In 1979, two McKinsey consultants, Tom Peters and Robert Waterman, developed a new way to describe an organization. They developed the 7s model, where a company is described as three impersonal and four interpersonal elements. (Figure 4) They defined strategy, structure and systems as the 'hard' impersonal elements, while style, skills, staff and shared values were described as the 'soft' interpersonal elements. (Waterman et al. 1980) By describing the organization through the 7s model, we will better understand how the organization works and how the several factors interact.

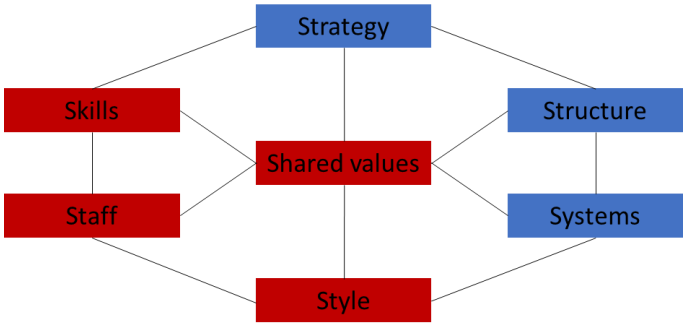

Figure 4 - McKinsey's 7S model, with the 'hard' elements depicted in blue and the 'soft' elements depicted in red.

Structure

INVITROM is a learned society that promotes the academic discipline of *in vitro* biomedical research. Membership is open to all who are interested, with mostly scientists attending their events, but also others. INVITROM is an international society, with most of their members and all of their board are located in the Netherlands and Belgium. They are registered in the Dutch Chamber of Commerce, number: KvK 17195487.

Systems

INVITROM uses many systems as part of their general operations. First off, they use a website, http://invitrom.org/, as a main platform for everything involving their organization. Here you can find what they want to achieve, and how they want to achieve this, as well as a page where you can sign up to become a member or sponsor of the organization. There is also a form that can be used on the website to contact the organization for other inquiries. For members, the functionality of the website expands to give them access to financial records, as well as presentation documents and photos from symposia and workshops organized by INVITROM. Through the membership sign-up page, they collect email-addresses of all members, which are added to their private email-list. They use this list for communications about the society as well as announcements surrounding their symposia.

They currently organize a symposium annually, with a changing theme within the field of *in vitro* biomedical research every year. INVITROM currently uses sponsorship as well as an annual membership fee as a means of revenue generation for their organization. They do not ask a fee for Master-students, PhD-students or technicians, but do require a membership in order for people to attend their annual symposium. They collect membership/attendance fees by means of pay-pal and bank transfer. This has proven to be a bit of an issue, as some attendees still to pay have their due fees even after many reminders by the treasurer.

Style

INVITROM has an informal, approachable attitude. This can be seen throughout the organization. The members of the board all work for INVITROM as volunteers next to their jobs as researchers.

Staff

INVITROM doesn't employ any staff members. Their executive board consists of 6 people, who all have taken their roles voluntarily next to their work as researchers. 2 of these members are PhD-students, which adds to INVITROM's interest in young researchers. They have a chairman, Prof. Dr. Peter Olinga, and a treasurer, Dr. An van Rompay. Furthermore, their board includes a secretary, Dr. Nynke Kramer, and officially also a sponsor liaison, Dr. Rita Cortvrindt, although her involvement with the organization is unclear at the moment. In the meantime, PhD-student board members Gerian Prins and Joost Boeckmans have been appointed to be responsible for sponsors. The board of INVITROM is quite dynamic. According to the statutes a board member is appointed for the time of 4 years, with possibility of reappointment once. A board member may be president for only one four-year term.

Skills

INVITROM is an organization made up of and for biomedical scientists. Although the disciplinary fields they work in differ, they all are trained scientists who work as researchers for universities or other organizations. Many of the members are involved in improving biomedical sciences in accordance to the three R's, aiming to reduce, replace and refine animal experiments in biomedical sciences. During the 2018 symposium, one of the board members, Gerian Prins, was voted to have given the best young scientist speed presentation by all attendees.

Strategy

INVITROM aims to promote the development, application and acceptance of *in vitro* methods in biomedical research. To achieve these goals, they want to exchange information among professionals involved in these three goals. They try to stimulate collaboration between research institutes and industry, as well as inform regulatory bodies. Currently a focus on young scientists is an important part of INVITROM's strategy, as they have decided that for their 2018 symposium attendance for Master and PhD-students is free. Through this they expect to have more people in attendance, which could improve interaction and overall success of the symposium. When the symposium is a success, these younger generation of scientists could remain involved with INVITROM, attending symposia in the future as well as other events they might host.

Shared values

INVITROM was founded on the belief that the development, application and acceptance of *in vitro* models and methods should be improved. All members share a passion for *in vitro* biomedical research and enjoy discussing this work with their peers. They believe *in vitro* methods should play a bigger role in today's world, scientific and possibly beyond. Furthermore they believe it can be challenging to find time to discuss this work, as it can sometimes be challenging even amongst themselves to arrange for a meeting to discuss matters that are important to the organization.

Describing the essence of the annual symposium

Event scope, format, purpose, concept:

The annual INVITROM symposium aims to stimulate collaboration and information exchange. The annual symposium has always had the same overall goal, to inform everybody on the new developments within the field of *in vitro* biomedical research. The exact theme of the symposium changes every year. Each year a number of speakers is invited to discuss their work in plenary sessions, while anyone interested is encouraged to present a poster discussing their work at the symposium. The symposium offers a variety of breaks, in which networking and discussing posters is encouraged.

Event marketing: The 4 P's of marketing

Next to the organization, it is important to take a look at the annual symposium INVITROM organizes. To do so, we will describe the symposium according the marketing mix' 4 P's below. The marketing mix is usually used for strategizing the marketing of a product. (McCarthy 1960) Here we will adapt it to be used for the assessment of the annual symposium. According to the marketing mix, there are four aspects to consider when assessing the qualities of the Symposium: Product, Place, Price and Promotion. By describing the symposium according to these measures, it allows INVITROM not only to get a better grasp of what they are offering exactly, but also how this can be communicated best with their audience. The symposium is not simply the offer of informative speakers for an entire day. Instead, for symposia and conferences the 4 Ps should be considered in the sense of how the different aspects can contribute to or inhibit the overall experience, which will help sell the value of attending the annual symposium. (Edwards et al. 2017)

Product

When considering the symposium as a product, the quality of the product will be largely dependent of the speakers supplying INVITROM with content at their symposium, through either a complete speech or a poster presentation during sessions. It is of vital importance to this aspect that the members of the board use their networks optimally, to find the speakers who are best suited to the theme of that year's symposium. The other part that can be very important will be the amount of people attending. As part of the value of the annual symposium is getting to interact with colleagues within the field of *in vitro* research and possibly even start new collaborations. How much this happens will most certainly depend on how many people attend the symposium.

During the 2018 symposium speakers where scheduled for approximately 40 minutes, with about 30 minutes of presenting and 10 minutes for discussion and questions. I believe this is an appropriate way to use the speakers, as it allows for a short and to the point story and through that, there can be a lot of discussion, either during the 10 minutes or during some of the many breaks during the program.

Place

Another very important aspect for the symposium is the place. This can distilled into two separate aspects, both the geographical location as well as the ambiance and quality of the actual accommodation.

Geographical location is a strength of INVITROM

Firstly, INVITROM currently resides in the Netherlands and Belgium. This is an excellent location for a learned society of biomedical sciences to be established. Almost all Dutch universities are considered to be in the top 2% of universities worldwide, according to four of the most used university rankings. (Table 4) Furthermore, Dutch publications rank second in publication citations. This location also adds to the international perspective for INVITROM, as 14% of all students and 36% of all researchers at these universities are international. Not only do these researchers do exceptionally well in terms of citations, but they collectively also rank 2nd in number of publications per researcher. (Vereniging van Nederlandse Universiteiten 2018)Although on average Belgian universities have a little lower ranking, they do have universities outperforming Dutch universities according to some of the ranking lists. (Table 3) After INVITROM has considered in which city they would like to host the next event, it can be useful to get in touch with the local convention bureau, which can help them identify the best location for their event. It could also potentially help them spread awareness among conference and symposia enthusiasts. As mentioned before, Belgium and more so the Netherlands score very high on several of the University rankings, which provides them with ample opportunity to have a good location from the development point of their mission. Other locations could include regulatory agencies or grant organizations such as the Dutch Organisation for Applied Scientific Research (TNO), Dutch Organisation for Healthcare Research and Innovation (ZonMW) as well as the Fonds Wetenschappelijk Onderzoek (FWO), Federal Knowledge-center for Healthcare (KCE), Flanders Organization for Technological Research (VITO) and the Flanders Institute for Biotechnology (VIB).

Table 4 - Rankings of Dutch and Belgian Universities according to the Academic Ranking of World Universities (ARWU) (2017), Times Higher Education (THE) (2018), Quacuarelli Symonds (QS) (2018) and the Centre for Science and Technology Studies Leiden (CWTS) (2017). NR = Not ranked

Dutch Universities	ARWU	THE	QS	CWTS
Erasmus Universiteit Rotterdam	73	72	147	75
Radboud Universiteit Nijmegen	101-150	122	204	88
Rijksuniversiteit Groningen	59	83	113	147
TU Delft	151-200	63	54	66
TU Eindhoven	301-400	141	104	133
Tilburg University	NR	195	357	296
Universiteit Leiden	88	67	109	90
Universiteit Maastricht	201-300	103	200	134
Universiteit Twente	301-400	179	179	180
Universiteit Utrecht	47	68	109	61
Universiteit van Amsterdam	101-150	59	58	64
Vrije Universiteit Amsterdam	101-150	165	218	93
Wageningen University	101-150	64	124	84
Belgian universities	**ARWU**	**THE**	**QS**	**CWTS**
Universiteit Gent	69	107	125	55
Katholieke Universiteit Leuven	90	47	71	47
UC Louvain	101-150	129	153	313
UL Bruxelles	151-200	175	205	370
Universiteit van Antwerpen	201-300	201-250	210	353
Vrije Universiteit Brussel	201-300	301-350	182	429
University of Liege	301-400	301-350	319	363
Hasselt University	NR	401-500	NR	NR
University of Mons	NR	NR	551-600	NR

According to the Global Innovation Index, the Netherlands ranks 3rd in the international innovation rankings. Their report goes on to say that the Netherlands does not only spend a lot on innovation, both publicly and privately, but they also perform higher than expected at their current expenditure rate, ranking 4th in efficiency. (Cornell University et al. 2017) This all indicates a cultural advantage for innovation in the Netherlands. Cultural advantages do not only make a country a better suited place for innovation to take place, but also the advantages of these cultural values also operate on the organizational level. (Shane 1992) This all makes the Netherlands a very attractive region for scientists as well as businessmen. It also indicates that the presence of Dutch members within the board of INVITROM can be seen as an advantage for the organization.

Ambience and quality of the venue

Whichever location INVITROM decides upon, they must ensure that the accommodation fits the needs for the organization of the symposium. They have to have a comfortable plenary room that can fit enough people during programmed speeches, while they also need a break room and space to place boards for poster sessions. Another important aspect that gets overlooked quite easily is the space for parking for the commuter audience. During the 2018 symposium some of the plenary speakers had trouble finding parking space, which almost made them late for their lecture. Any accommodation INVITROM would like to use must fit the criteria for the elements listed in table 5.

Table 5 - A checklist INVITROM should run through to see if their proposed venue contains the minimal criteria to be suited for their symposium. (Adapted from Hoyle 2002)

Good venue location checklist
Proximity to the potential attendees and ease of travel
Availability of parking for a commuter audience
Ambiance and originality of the site
Logistical practicality of staging a particular event
Surrounding attractions/infrastructure for additional activities
Existence of related audiences, organizations
Degree to which the location fits the character of the event
Safety, security of event attendees
Availability of public transportation

Price

INVITROM is trying to put attendance and experience before financial benefits in terms of price. For the first time during its long run of symposia, INVITROM has decided to no longer charge Master students, PhD students and technicians. This will allow for a lower barrier for these students and technicians to come and not only attend the symposia, but also present some of their work. This could potentially give INVITROM additional content, while also increasing attendance. However, the drawback is that this could potentially reduce income, as all who fit these criteria who previously attended will now no longer provide INVITROM with the attendance fees. The first symposium in which this strategy was implemented saw an increase in attendance from 28 people at the 2017 symposium to 53 at the 2018 symposium. By increasing attendance, the experience for everyone attending is likely to improve. For others interested, attendance costs 35€, which includes a year membership of INVITROM. For new attendees this is a reduction, as INVITROM used to charge 50€ for first-time attendees, and 35€ for returning guests. When comparing this to some of the other symposia within their field, this is a very low price.

Promotion

Currently, INVITROM uses their email list to send out promotional messages for their annual symposium. Furthermore, the members of the board put up posters and flyers at their respective workplaces. The result of this is that the promotional material for this year's annual symposium was mainly sent out to researchers at universities, as most of the board consists of university researchers. Some important groups of potential interested people were therefore missed: Businessmen and government officials.

INVITROM should consider the time they give their promotion efforts. Although I believe the promotional material was of good quality, they probably were sent out too late to reach their complete potential. It will be important for INVITROM to maintain low level engagement with members and attendees throughout the year, and to notify them early of the next symposium. This way they allow their guests to ask permission from their bosses, or possibly even encourage them to also attend, while also giving the possible guests time to assess whether they want to come or not. Sending out promotional material could start 6 months before the symposium takes place and could use 1 to 3 emails per month, depending on how much new information is available for the potential attendees and how much time there will be left to register for the symposium. This tardiness is even more an issue when considering sponsorships, which will be discussed in a later chapter.

Marketing strategies

One of INVITROM's main resources is their email list. They use this list to provide members with information and to promote the annual symposium. It is very important that INVITROM considers the purpose of the email they send. INVITROM could implement a monthly newsletter, where messages would mainly be about informing the members of INVITROM about some of the activity surrounding the field and the organization. By implementing this, they would have year-round content for their members and keep some engagement with them until the next symposium arrives.

Using the AIDAS model for marketing communications for the annual symposium

For mail intended to get more people to attend the annual symposium, INVITROM should consider the AIDAS model when developing promotional material regarding the symposium. Attention, Interest, Desire, Action and Satisfaction. The AIDAS model suggests a promotional message should have a structure, where each of the first four letters of the AIDAS model is followed by the next. (Strong 1925) Using the AIDAS model will make marketing communications more effective and could increase the amount of repeating attendees. This model is also suitable to increase the amount of responses on evaluation requests, as these are then the action of the AIDAS.

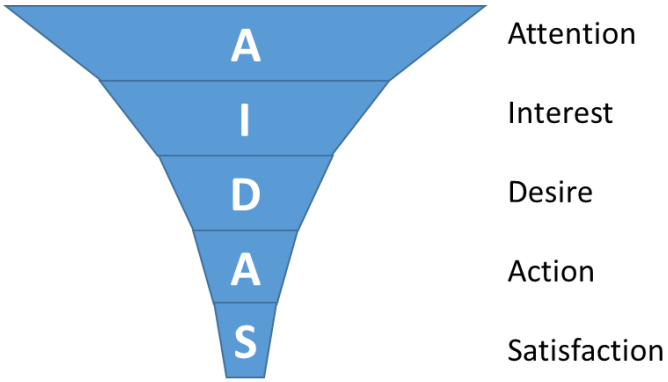

Figure 5 - Schematic representation of the AIDAS model. With every step some readers might lose interest, while some end up not only buying (Action), but also enjoying and recommending the product to peers (Satisfaction).

Attention should be considered specifically when thinking of the title and first paragraph of the email. It should contain exciting new information that can persuade the reader to read further. Then the potential attendee's interest could be awakened by information about speakers, themes and other useful and interesting information about the symposium. Specifying the event's target market can also help here, as it will increase the appeal for anyone who associates themselves with the audience mentioned. Next, creating desire for attending the symposium can almost come naturally, in the form of a question p.e.: 'Do you want to know about the exciting new developments within the field of in vitro methods, while discussing them with many of your peers?'. Usually the action for the symposium will be registry, which flows naturally from the aforementioned question and can easily be hyperlinked into the email. Finally, and most positively, if the customer is satisfied (The S of AIDAS), he or she will become a returning attendee and will promote the event to his or her colleagues and anyone who they know could be interested. This is something that INVITROM should actively encourage attendees who plan on coming next year. Satisfaction for evaluation requests could also include a small incentive, a discount for next year's event i.e.

Additional marketing tools

Next to the methods currently employed, INVITROM could try to use other marketing tools. These could include TV or newspaper advertisements, digital marketing (via google AdWords i.e.) or radio or TV commercials. (Hoyle 2002) However, considering the budget INVITROM has and the nature of the event, I think most of these methods would not be suitable for INVITROM as of right now. Because the annual symposium and organization should thrive on social interaction, using social media might be beneficial and it is cost-free. With a big group of social media platforms available, Facebook and LinkedIn seem most suitable, as they allow for privatized groups and are still used by everyone. When attendance and income increase, marketing tools could be expanded. I believe digital marketing would be the way to go, as most researchers are so dependent on the internet nowadays. Furthermore, most digital marketing platforms allow for very direct targeting, by search queries i.e., which would be beneficial for INVITROM because of the saturation of the market they are in. Because Google is still the most used search engine, also specifically in the Netherlands and Belgium, I think using a Google program such as Google AdWords would be most efficient. (Statcounter.com 2018)

External and market analysis

Market analysis

The BioTech and Life Sciences business markets in the Netherlands and Belgium are quite large

There are an astounding 455 BioTech companies in the Netherlands in 2018. (BioTechGate 2018) The average revenue of these companies has been quite stable. Between 2010 and 2014, there was an increase in revenue of 0.8%, increasing the annual revenue in 2014 to $352.1m. This is expected to increase with a compound annual growth rate of 4.7% until 2019, which would put the revenue at approximately $441.9m in 2019. (Researchandmarkets.com 2015) In Belgium there are currently over 140 BioTech businesses. They generate 16% of the European revenue, while using only 10% of the European R&D expenses. (Belgische Federale Overheid 2018)

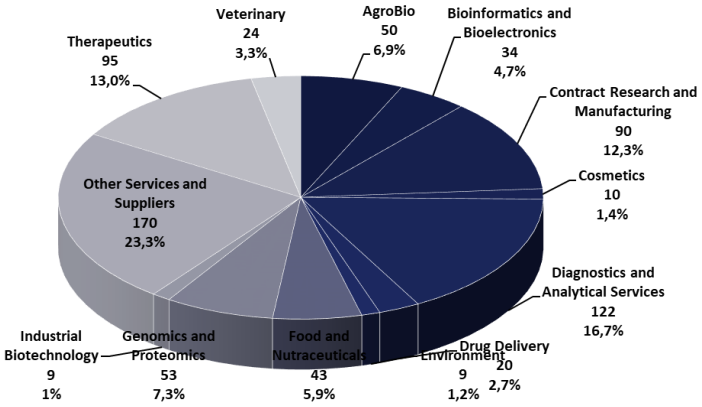

Figure 6 - Key activities of BioTech companies in the Netherlands. (BioTechGate 2018)

The BioTech business market in the Netherlands focusses on supplies and oncology

In the Netherlands, the key activities of the BioTech sector are very diverse. Most companies venture into supply and other services, while diagnostics and analytical services are second. Furthermore, contract research and manufacturing and therapeutics take up 13% of the industry. (Figure 7) Together, these 3 make up over 60% of the entire sector. When looking at the distribution from a different perspective, based on therapeutic area, most companies work on cancer, followed by infectious and parasitic diseases and neurological disorders. (Figure 8; BioTechGate 2018)

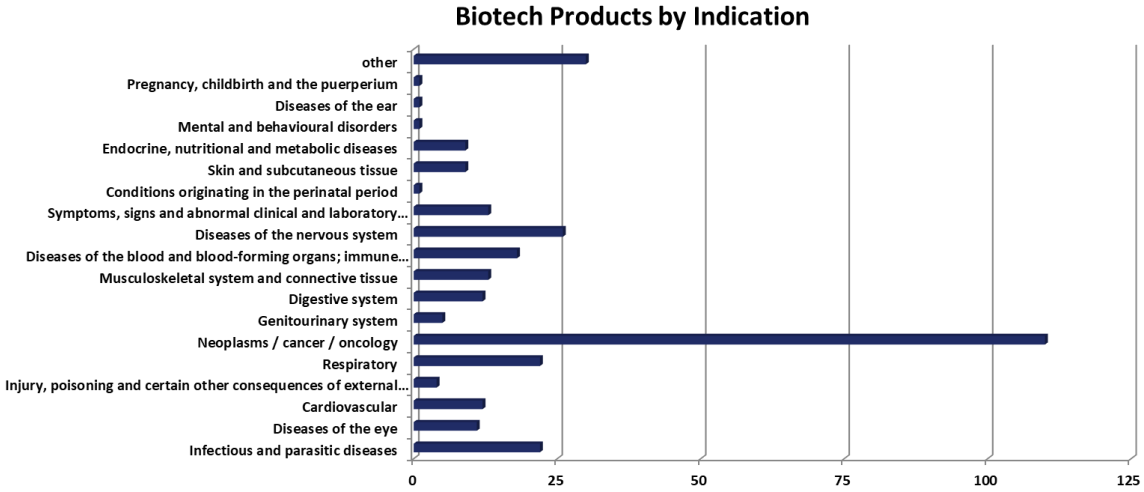

Figure 7 - BioTech product distribution by indication (BioTechGate, 2018)

The association meetings market in the Netherlands and Belgium are large

The international associations market has steadily increased over the last decades. From 1963 to 2012, the number of meetings have exponentially increased, even through some tough economic times. Furthermore, during this time, the number of total participants has increased exponentially as well. (ICCA 2014)However, the average amount of participants per meeting has steadily been decreasing, meaning the meetings have become more abundant, but smaller. When looking at the Netherlands and Belgium, we find them ranked 10th and 19th in number of meetings held, with 307 and 208 meetings respectively. (ICCA 2017) Diving even deeper into the market, 1 Dutch and 1 Belgian city rank in the top 30 cities to host meetings worldwide. Amsterdam hosted 112 meetings in 2017, while Brussels hosted 90. (ICCA 2017)Amsterdam has been one of the top cities to host association meetings for years. (ICCA 2014)Overall the size of the meetings in the Netherlands has followed the trend found worldwide, with an estimated average of 438 participants per meeting in 2017. (ICCA 2017)

Describing the attractiveness of the scientific events market: Porter's 5 Forces

Naturally, the size and distribution of the markets INVITROM is involved in do not describe the complete environment where INVITROM is operating. In 1979 a man named Michael E. Porter described the 5 forces that shape business strategy. Although it was his first publication in the Harvard Business review, it immediately started a revolution in the field of business strategy. By analyzing the 5 forces Porter describes (Figure 9) a strategist can get a good idea of the nature of the field that the organization is operating in. (Porter 1979)

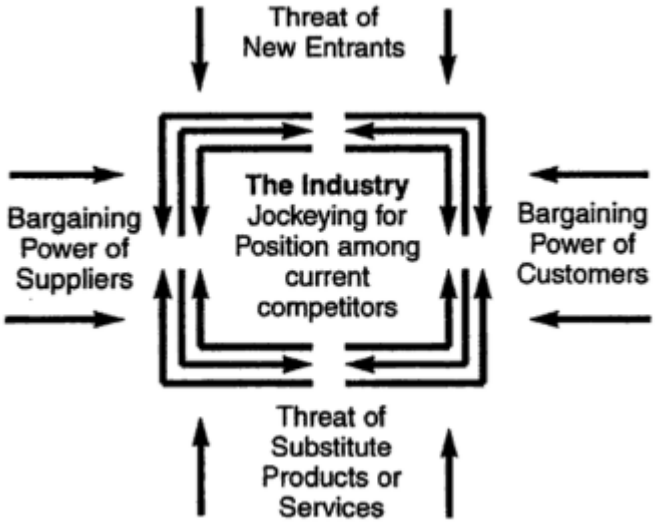

Figure 8 - Porter's 5 forces model (Porter, 1979)

Some buyers and suppliers are the same for INVITROM and have high power, while other suppliers have quite low power

In his five forces model, Porter distinguished two forces that either buy the product, or supply means necessary for the product: The buyers and suppliers. The idea is that when buyer or supplier power becomes too high, it reduces the attractiveness of a certain field. Buyers can have high power when they are very concentrated and can have a lot of choice of where to buy the product. This means there is more effort needed to persuade potential customers to buy your product. Suppliers can have high power when they are very concentrated. Per example, if there was only one place where scientists would be working in Europe, one university, then the potential suppliers of content for a symposium have a lot of power: They are the only ones that could do this.

For INVITROM, this part of the 5 Forces analysis is actually a bit different than the theory. This is because the buyers are also part of the suppliers. When considering attendees, aside from students and technicians, they pay to attend the symposium. They buy rights to be at the gathering, to hear the plenary speeches and to get to network with other attendees. However, they can potentially present a poster and offer value for other attendees through networking, which makes them suppliers. For sponsors, essentially the same holds true. They pay INVITROM for rights to attend the symposium, to promote their products and network with attendees. But they also provide content in the form of interesting products for attendees and also the networking opportunity. I think that because of this their power reduces. That doesn't mean they don't have any power, as the attendees and sponsors are a big part of any event's experience and they can always choose to go to a different event or no events at all.

Another supplier for INVITROM are the speakers. They provide interesting content for the event and are an important part in one of the main goals: Informing the audience. Their power can potentially be quite high, as the overall experience will be less attractive when there are no interesting speakers. However, due to the high number of researchers at various venues in both the Netherlands and Belgium, there are many suppliers to choose from in this setting. Therefore speakers do not have high power.

Other suppliers for INVITROM include venues and catering services. Venues supply INVITROM with space, audio-technical tools for the plenary sessions and usually poster boards for the poster sessions. Catering services provide coffee, tea and any refreshments for the symposium. These have relative low power as there are many options available. Some venues might have their own catering service, which you are obliged to use when using their venue. This gives them some power in this regard, but I don't believe this will make a huge difference compared to a venue where you are free to use any catering service. It also removes the activity of finding a catering service to use, leaving more time to work on other aspects of the symposium.

There are many substitutes available, but none have proven to be very effective when it comes to stimulating collaboration.

There are many things that could be considered a substitute for INVITROM's annual symposium. Information exchange has increased dramatically since the dawn of the internet and as a result, it would seem that informing audiences has become less and less of an important part of symposia. Furthermore, social media such as Skype, WhatsApp, Facebook and LinkedIn have made it much easier to meet and talk to people online, which seems to further damage one of the values of symposia. However, as the results discussed above showed, the amount of association meetings is still increasing. This shows that although there might be substitutes for the supply of information, there is still a need for personal meetings that is filled by symposia and conferences. The notion that the meetings overall get smaller, could indicate that there is a chance to meet most people attending. This would suggest that the interactions between colleagues is becoming more important, which seems to be easier or preferred at a conference than through the internet.

There is a high threat of new entries

Unfortunately for INVITROM, the treat of new entries into the market is very high. First of all, the budget needed to organize a similar symposium is not quite large. With INVITROM having a budget of between 2000 and 3000 euro's for their symposium (Appendix II), the amount of money needed to organize a similar one is not very high. Furthermore, any of the other parts of the organization, like the website or email-list, could be easily obtained, as websites are built more and more and for lower prices, and harvesting email-addresses through them is not at all challenging anymore. When looking at the Dutch and Belgian governments, they openly admit that they think academic symposia are important and offer support in organizing them, meaning they do not offer any entry barriers for potential new entrants. However this does not necessarily mean that anyone could organize similar events. In order to understand the needs and wishes of academics, it would be much harder for someone with no prior background in academics to organize a similar event.

Describing INVITROM's main competitors and how competition works in the field of scientific events

A main competitor that immediately pops up is the 3R's centre in Utrecht. It's an organization related to the University Utrecht. Their activities revolve around the development, application and acceptance of 3R methods in biomedical sciences. This makes them very similar to INVITROM. They currently consist of 6 employees, all also associated with the University Utrecht. Their project-manager is a former chairman of INVITROM: Dr. Jan van der Valk. Their main product is a free available database consisting of 3R-supporting methods. Furthermore they are involved in graduate-level education and they try to inform anyone interested about the developments in the field. This is very close related to the mission of INVITROM. (3Rs-centre ULS 2018)

Another competitor of INVITROM is the European Society for Toxicology *In Vitro* (ESTIV). They claim to be the leading organization in Europe that strengthens the networks of *in vitro* toxicology and promotes it, both educationally and scientifically, in all European countries. Furthermore, they aim to strengthen scientific networks and facilitate communication between academia, industry and regulators. They organize a symposium every two years and are regularly involved in educational and scientific events to promote *in vitro* toxicology. They also publish a scientific journal: Toxicology *in vitro* which comes out approximately 7 times per year. They list INVITROM as an affiliated organization on their website. Although they do not list any membership numbers, based on the size of their symposium (4-5 days) and the amount of other events they host, it is safe to assume they are a much bigger organization than INVITROM. Their focus is on *in vitro* and *in silico* biology, but only in the field of toxicology. (ESTIV 2018)

On a worldwide scale one of the biggest competitors for INVITROM is Society for *In Vitro* Biology (SIVB). Their organization focusses on all *in vitro* biology. Not just human biomedical research, but also other animals and plants. They publish two journals: *In vitro* cellular & developmental biology – Animal (10 times annually) and *In vitro* cellular & developmental biology – Plant (6 times annually). Furthermore they organize a 5 day symposium every year, where all previously mentioned aspects of *in vitro* biology are represented. They have collected a set of websites that contain protocol databases for anyone to use. They also promote several other events, and invite anyone to send in their events to be put on their website's events-calendar. (Society for In Vitro Biology 2018) According to their 2017 annual report, they have a positive financial position, mainly due to their journals. Their net assets at the end of 2017 were $594,669. (Tomes et al. 2017)

Another big player on the worldwide stage is Keystone Symposia. This 501(c)(3) non-profit organization is dedicated to organizing scientific symposia and workshops in the field of biomedical research and life sciences. In collaboration with scientists they give rise to approximately 50-60 conferences each year, all over the world. They do not have a specific focus beyond biomedical and life sciences research. They believe by connecting scientists within and across different fields, they will contribute to the generation of new ideas, exchanging information and acceleration of applications that will ultimately benefit society. (Keystone symposia 2018) They are not only the biggest competitor in terms of amount of events organized, but also in terms of finance, as their net assets on the 30th of June 2017 were $16,922,683. (Keystone Symposia Board of Directors 2017)

Many cross-promotion opportunities can provide extra content during down months

The competitors mentioned above already indicate that the field of scientific symposia is very large. The list could be even larger, as mentioned before when discussing the international markets meeting. However, this does not actually mean that there is much competition. Within the field of scientific symposia and congresses, most organizations are interested in advertising other events related to their subjects. This provides INVITROM with an easy way of promoting their events among untapped markets. Next to the competitors mentioned above, the Dutch Life Science Database is also interested in adding events pertaining the life sciences to their events-calendar. HollandBio, the Dutch association for BioTech companies, also has an events calendar on their website.(HollandBio 2018) Their calendar includes events from organizations who aren't directly involved with HollandBio. Finally, the institute for human organ and disease model technologies (hDMT) also actively promote events on their website. (hDMT 2018)

The lack of competition in the sense of promotion does not mean that there is no competition at all. Because many events will have overlapping themes, INVITROM will be competing with these other events with regard to speakers. This could give INVITROM a little bit of a challenge, as all of the speakers they might want to have at their symposium could be otherwise engaged or already attending a lot of other events, making them less interesting for INVITROM. However, because there are many great scientists in both the Netherlands and Belgium, I expect INVITROM not to have too much problems finding interesting speakers for their symposium.

Charting the needs and opinions of the INVITROM members using posters and Mentimeter

During the annual symposium many members, old and new, were together in one spot. This makes it the perfect moment to ask the attendees some specific and general questions about the organization and its symposium. Both to get a better understanding of the issues that the attendees face, as well as to get an idea of the attendee's wishes and ideas for INVITROM. We used four posters which posed general questions, where attendees could use post-it notes to leave suggestions. (Appendix III) The questions posed by these posters can be used every year, to generate more ideas for INVITROM and assess attendee wishes. More specific questions were posed using Mentimeter at the start of the first plenary session. These questions could also be used every year. (Appendix I)

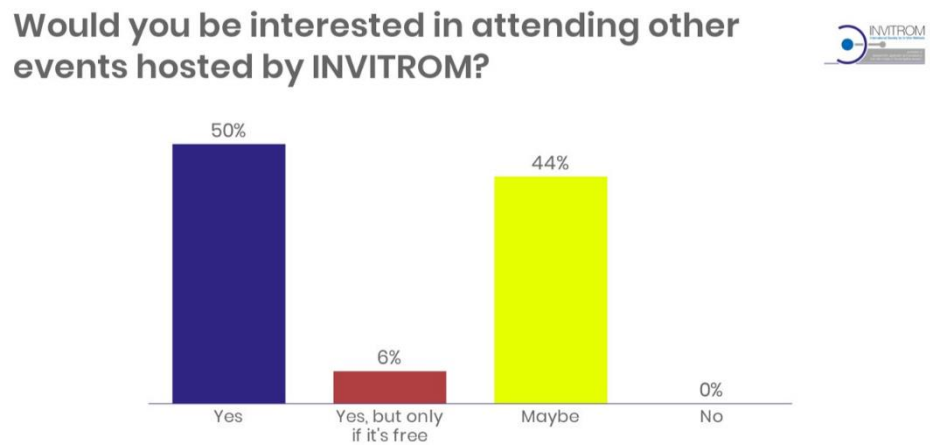

Figure 9 - One of the results from the mentimeter polling done at the 2018 annual INVITROM symposium.

Considering the posters we used, it was very obvious that the attendees where attending the annual symposium to be informed about the latest developments within their field. Almost all contributions to the poster asking for their reasons to attend the symposium stated this. Furthermore, results from the posters and Mentimeter showed all attendees to some degree had interest in attending other events that INVITROM could host. Most suggestions for other events were focused on interactions, ranging from a mixer to speed dating to get to know more people. Other suggestions included workshops and trainings. One thing that also stood out is that according to the attendees there was a lack of publicity for INVITROM this year.

To increase response on these evaluations, as well as make it more of a contribution to the event experience, INVITROM could choose to add an incentive to contributing. By p. e. using a small prize for the best suggestion/idea on the poster, you motivate people to give suggestions, while making it contribute more to the overall experience for the audience instead of it subtracting from the event experience, which is something that is a general concern with evaluations.

Sponsorship & funding

In this chapter, we will discuss how INVITROM could improve their sponsorship seeking strategies. Furthermore, we will get into other means of funding that could help INVITROM raise funds in the future.

Using sponsorship as a means for funding

Sponsorship has been used for years as a strategy by many companies to get more attention from target audiences. Specifically, sponsors like Pepsi or Coca Cola have been involved in the organization of major events such as the Super Bowl, the soccer World Cup or the for ages and with success. Typically, the sponsor wants to connect with a target audience, and uses the sponsored event as a conduit to reach that target market. INVITROM provides a potential sponsor with just this: An opportunity to connect with researchers working with *in vitro* methods.

Adapting a new sponsorship seeking strategy

Previously, INVITROM had one board member dedicated to finding sponsors for the annual symposium. According to the previous sponsor liaison, it was very challenging to find sponsors based on so called cold calling, where she would simply try to get in touch with potential partners without any previous connections. This is a very outdated method of sponsorship finding. Current practice dictates that sponsorship finding is best done within the networks of sponsor searchers, where there is already a connection established. (Skildum-reid 2016a) Also, it is important to see sponsorship as an important part of the organization as a whole. Although basic work, like standardized packages and promotional material could be developed by one person, every member of the board should reach out to organizations within their network who could contribute to the annual symposium as a sponsor. (Skildum-reid 2016a; Skildum-reid 2016b) Through this approach, you can reach a far bigger group of leads, while getting more success by embedding sponsorship in the entire organization, as opposed to one person working on it. It is to be noted that this approach does not necessarily increase the workload of the board members. Because previously established connections are being used, INVITROM simply has to be in the back of a board member's mind when in touch with any of the potential leads, keeping the needed effort relatively low.

Understanding the potential sponsor

When considering possible sponsors, it is very important to investigate the background of the company you are considering. In order for a sponsorship to be fruitful and a positive experience for both the sponsor, sponsee and attendants, the goals of the sponsors have to be in line with some of the goals of the sponsee and attendants. If this is not the case, then any sponsorship is much more likely to be ineffective and most sponsors would not endeavor in these types of activities. By finding common interest between the sponsor, sponsee and attendants you can effectively communicate with the potential sponsor how sponsoring the event can benefit them. For INVITROM, this means that the goals of the companies they want to reach out to for sponsorship need to have something to do with their mission.

The types of companies that fit well with INVITROM's goals

One type of company that immediately catches the eye is scientific supply companies. By developing new machines that can be used easier or allow for more effective studies, they could contribute to the development of *in vitro* methods. Bringing attending researchers in touch with these companies will contribute towards their mission. Therefore, any good scientific supply company would be a good fit, both for that company, INVITROM and their shared target audience. A nice benefit of these companies is that they usually offer different types of supplies, meaning e.g. a company selling cells for experimentation could be a sponsor, while a company selling a culturing machine could be a sponsor at the same time as their target audience is similar, but their products are not. Also, because INVITROM operates within a field that will help reduce animal experimentation, animal welfare organisations such as Proefdiervrij or even the Dutch Society for the protection of animals (De Dierenbescherming) could potentially sponsor INVITROM. (Proefdiervrij 2018; Dierenbescherming 2018) Of these two, Proefdiervrij seems more suitable, as their goals align more directly to those of INVITROM than those of the Society for the protection of animals and Proefdiervrij is already part of the board's network. One small sidenote for these companies is that it might be harder for them to directly contribute to the event experience, as I do not see any way they will directly appeal to many researchers. However, I am sure that this could be explored during negotiations.

Individual attention for each potential sponsor is very important for successful sponsorships

It is important to make specific individual cases for each potential sponsor, if you want your sponsorships to be successful. Although the companies INVITROM can approach can be quite similar, both in operations and in strategy, it is important that you consider the individual characteristics of each sponsor lead to increase the chance of successfully acquiring this sponsor. By showing you understand them as an organization they will most certainly be more interested in sponsoring as opposed to you giving them a standardized pitch that you have given to other companies hundreds of times. Furthermore, INVITROM shouldn't be afraid to let the sponsor come up with ideas of how to contribute to the event. As we discussed above, INVITROM and the sponsor will share a target audience and it is very likely that the sponsor will have good ideas on how to reach that audience. This could then help the sponsor contribute to the overall experience at the event, which is the type of benefit INVITROM should be looking for with sponsors.

SMART Goal setting for sponsorship

In order to make sure the sponsorship seeking does not get out of hand, it is important to set goals before INVITROM starts looking for sponsors. In order to make sure that the goals set for sponsorship fit INVITROM, they can use the SMART goal setting. It will help structure and measure the goals INVITROM sets for themselves. The acronym SMART stands for **s**pecific, **m**easurable, **a**ttainable, **r**elevant and **t**imely. Any goals INVITROM sets with regards to sponsorship should consider these 5 aspects. I believe INVITROM could at the very least be able to have 2 sponsors every year. These sponsors could come from a variety of sources, but can provide them with up to €1000,- according to their current offers. Considering the size of the market and the skills of the board, this should be very attainable. Getting enough sponsorship is very relevant to the organization, as it will help them organize symposia for many years to come. It is important that the search for sponsors starts early. The moment the first details of the symposium are decided upon, the members of the board can start looking for partners in their respective networks.

Lessons to be learned from past sponsors

Although practices might not have been optimized, INVITROM does have some experience with sponsors at their annual symposium. However, contact with these sponsors has not been maintained throughout the years, making it hard to get in touch with them. For this report only one former sponsor was able to be reached despite many efforts to get in touch with others. Overall the sponsor was satisfied about the opportunity given by INVITROM. One general remark given was that there was not a lot of space for the sponsor's booth. The biggest take-away from the sponsor was that it was very unique that INVITROM offered sponsors the opportunity to speak. Specifically, the sponsor indicated this was something that alone was more valuable, and therefore was willing to spend more on, than simply having a booth all day at the event. Furthermore INVITROM could have increased the amount of people checking out the booth by introducing something as an incentive to visit all attending sponsors.

Subsidies by the Belgian and Dutch governments can offer additional funding

In Belgium, the Fund for Scientific Research (FWO) offers subsidies for congresses. It could offer a challenge for INVITROM to meet some of the criteria needed to obtain these subsidies. One of them requires a registration fee for all participants, making it impossible to obtain this subsidy while INVITROM wants registration for technicians, master- and PhD-students to be free of charge. Also, this subsidy requires an expected attendance of at least 200 attendees, with at least 50% being from international origin. However, the other subsidy does not have these criteria, making it more attractive for INVITROM at the moment. However, at least two Belgian universities need to be represented in the organizing committee of the symposium in order to be eligible for entry. (FWO 2018) This means INVITROM would have to add a board member from a Belgian university other than the Vrije Universiteit Brussel in order to be eligible for this subsidy. However, personal communications with the board have shown that they already have this intent, making it probably less of an issue for the future.

The Royal Dutch academy of sciences (KNAW) used to award subsidy for congresses who have an international character and are organized in the Netherlands. This subsidy was an interesting opportunity for INVITROM. However, the grant was discontinued from May 2018 forward. Personal communications with the KNAW revealed that the grant would be replaced by a more centralized fund, which will merge several of the previous grants. This could then potentially provide INVITROM similar opportunities as the Belgian counterpart and the previous opportunity provided by the KNAW. (KNAW 2018; Personal communications(Appendix IV))

Some interesting other opportunities

The Boehringer Ingelheim Foundation offer funding for scientific symposia with a focus on young scientists. This refers to PhD and PostDoc fellows, which are already a part of INVITROM's board. Their goal is to stimulate cooperation between young and older scientists, which definitely matches up with INVITROM's attempt to get more PhD and master-students to their symposium. An added benefit is that the chairman of INVITROM has worked with this organization before, which could help them to get approval for a funding request. (Boehringer Ingelheim Stiftung 2018)

Another aspect for INVITROM was the loss of income due to the removal of the attendance fee for students and technicians. A company based in the United Kingdom can provide INVITROM with a grant for the purpose of maintaining this strategy, without losing income. The Company of Biologists is a non-profit publishing organization that uses their annual surplus to give out grants to scientists and scientific societies for a variety of causes, including reducing or waiving admission fees. They do have some additional terms to be met within the application and approval, including a summary of the event and acknowledgement of their support in printed materials and on the website. (The company of biologists, 2018)

Similar to the Boehringer Ingelheim Foundation and the Company of Biologists, Regeneron and the Society for Experimental Biology also offer grants to support scientific meetings. (Regeneron 2018; Society for In Vitro Biology 2018) Here a similar application form should be filled out and there are certain rules that have to be adhered to, which are included in the application forms.

Crowdfunding

Another interesting opportunity for funding for INVITROM is crowdfunding. Although INVITROM is an organization that supports the efforts of scientists, their focus within the field of replacement of animal experimentation offers them another opportunity. Society wants to put an end to animal experimentation, which is shown in various Dutch governmental documents. (NCad 2017; van Dam 2017) Furthermore, there has been an increased interest in the 3Rs of animal experimentation within the scientific community, which all points towards people with an interest in what INVITROM is working towards. People offering donations as a means of contributing is therefore not a very farfetched idea, while it would not cost INVITROM anything but time to set it up on their website. They could potentially even work with Proefdiervrij, as they regularly set up these types of crowdfunding efforts on their website.

IV. Integration

Integrating the findings of this report using Osterwalder's framework

When considering all the analyses above, the current business model that INVITROM uses to host their annual symposium is already becoming clearer. There are 4 essential aspects involved in any business model. (Osterwalder 2004) (Figure 11) The value proposition: What are we trying to sell? The customers: 'To whom are we trying to sell?' The needed resources and activities: 'How do we put this into practice?' And the revenue: 'How do we make money from it?' To get a better idea of how the different aspects align we can use a framework in which we can see how the several elements of the model align with each other. This will help clarify the business model. Also, it can help identify possible overlapping elements, critical success factors and key performance elements.

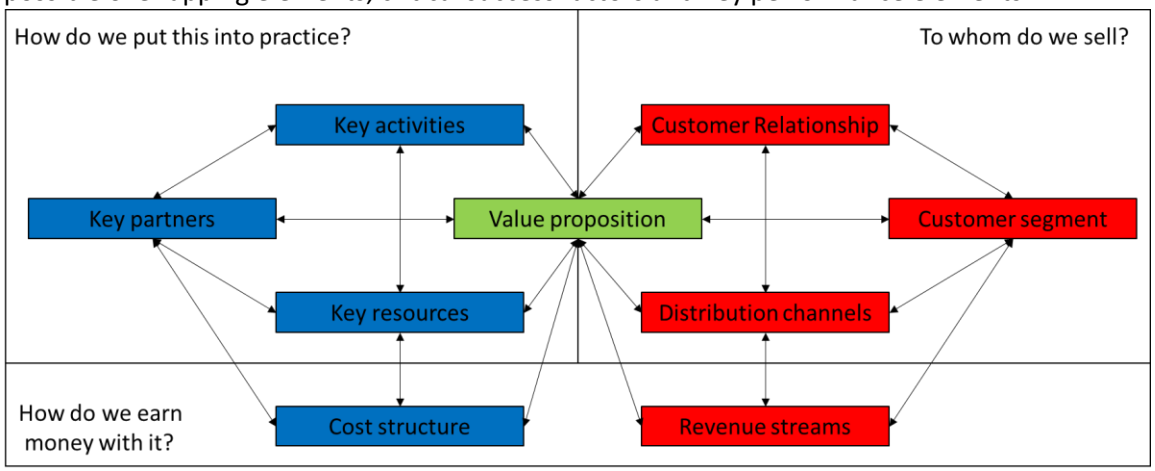

Figure 10 - A schematic view of Osterwalder's business model framework. (Based on an image found in Euverink, 2017)

INVITROM's current model

Using the analyses done above, Osterwalder's framework can be filled in for INVITROM. (Figure 12) One thing immediately apparent is that the current customer segment is very specific: Only *in vitro* scientists. Furthermore, the revenue streams could potentially be hazardous, as there are currently 2 streams of income, one of which was lacking at the 2018 symposium, sponsorship fees, while the other was lower due to the new rates for PhD- and Master-students. The absence of sponsors also means a missing key partner. If INVITROM was to continue down the exact path as they were in 2018, then this could potentially lead to budgeting issues, as there will be a lack of income compared to the costs of hosting the annual symposium.

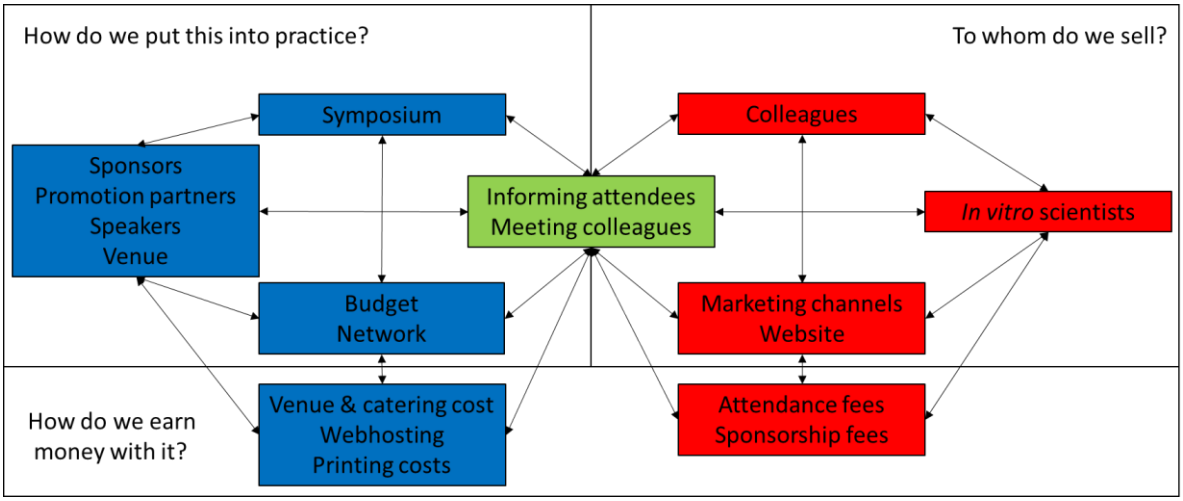

Figure 11 - INVITROM's current business model summarized in Osterwalder's framework

Some needed additions to the current model

Using Osterwalder's framework, some weaknesses in INVITROM's current business model were identified. But the analyses in this report offer some reinforcements to these aspects. (Figure 13) First off, in conjunction with their mission, INVITROM should aim to include BioTech companies (Possibly as sponsors) and government officials as part of their customer segment. This will help them by getting business and policy in touch with the scientists, but will also increase the attendance fees. They can further increase their income by moving their sponsorship seeking efforts to the next generation sponsorship, where they use their network to help find suitable partners. Additionally, they can seek subsidies from the Dutch and Belgian governments with relative ease and a variety of organizations also offer grants for organizing meetings and symposia that they can apply for. If this model will cause them to make too much of a profit, the organization should consider investing these profits by providing additional content and/or events for the members of the organization.

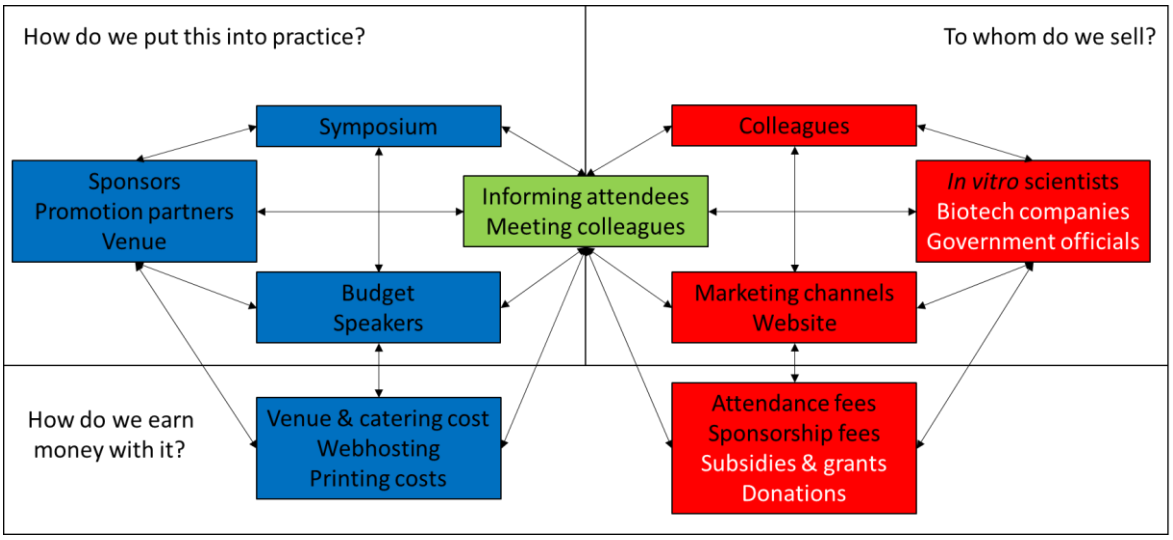

Figure 12 - Adaptions to be considered for INVITROM's business model, summarized in Osterwalder's framework

Two interesting topics: Neurobiology & Oncology

If we look at the scientific analysis and the business analysis it becomes very apparent that neurobiology has a lot of potential for INVITROM. It is one of the fields in which still many of the animal experiments are conducted, while *in vitro* alternatives are definitely present, especially with the rise of induced stem cells. Furthermore there are many businesses that work on neurological disorders, making way for added value for them directly through their topic, which can provide them a reason to attend the symposium. The multidisciplinary topics that INVITROM aims to provide will most certainly also then help people think of new and exciting ways to study neurological disorders *in vitro*. Another interesting topic might be oncology, as most of the biotech companies in the Netherlands are working within this field. This could provide INVITROM with even more business attendees.

Never lose sight of the essential aspects of symposia

INVITROM should be wary of return-of-investment ideology. Associations and symposia rely heavily on social interaction and intangible matters, which can set them apart. With technology ever expanding making it easier for us to access information at any given time, the aspects of social interactions are often overlooked. However, it is often these interactions that bring new insights, increase motivation and could cause new collaborations to be formed. By being aware of this, INVITROM can better communicate about the added value of their event, which can help promoting the upcoming events. They do not want to lose money every year, but because they have some money backed up to cover some losses, a year or two where they might spend more money than they earn will not have a big impact on the organization.

V. Recommendations

Start preparations earlier, finish preparations at least 3 months before the event.

The effort INVITROM put into organizing their symposium this year could potentially already have yielded more results. If the program and venues would have been organized earlier, with the same effort, potential attendees could have had more time to arrange for them to attend. An example is the fact that one of the board members was unable to join due to previous commitments. This could be the case for much more potential attendees, and by giving them more time to prepare, as well as having them put the event on their calendar earlier, the same efforts can reach maximum potential. Having everything arranged at least 3 months before the event-date gives the board members more time to find and negotiate with potential sponsors, and will give sponsors the time to evaluate offers internally.

Implement sponsorship seeking throughout the board

Current best practice methods for sponsorship seeking indicate that the best sponsors are found within the organizer's own network. The board used to have one person in charge of finding sponsors. However, by choosing to do so you essentially miss out on the opportunities that the networks of the other members of the board could provide. By making sure every board member thinks about which companies within their network could provide INVITROM with a good fit for sponsorship, they are able to maximize their potential and should be able to have at least 2 sponsors at every symposium from here on out. It is also important that these members talk to their respective networks themselves, as it is them the potential sponsor already knows and trusts, not necessarily the rest of the board. For this reason this advice does not focus directly on the potential companies INVITROM could approach for sponsorships. Personal communications with the board showed that the chairman already has contacts with Proefdiervrij and Boehringer Ingelheim, which would be a great place to start the search for sponsors for the upcoming year.

Invite businesses and policy makers to the annual symposium

Both to add to the experience of the symposium and to add more people from the industry, INVITROM should attempt to reach BioTech companies with their marketing efforts. I believe that companies that might not yet be part of the network of the board, but could provide INVITROM with sponsorship opportunities in the future, could simply be invited to come meet the members and experience the symposium for themselves. By showing what you're offering them, a company could be interested in sponsoring the event in the future. Furthermore, the addition of companies to the general audience could contribute to INVITROM's mission. Using the HollandBio database can help INVITROM reach out to the Biotech companies in the Netherlands. Addition of policy makers will add value to the event by giving experts a chance to discuss the issues they are facing with current policy, while the policy makers can get an update on the developments within the field of *in vitro* science.

Evaluate and get suggestions for the symposium, from both members and sponsors

Instead of having to think about which aspects from last year's symposium were very good, which still could use some improving or even which should potentially be lost for the next year, INVITROM should try to ask input from their audience. After all, they are the most important part of the event and also the reason for INVITROM to organize an event every year. I believe by using the posters and mentimeter survey developed during this project, INVITROM can somewhat track the experience from their audience, which will help them improve every year. The use of incentives for attendees to help evaluate and give suggestions could help increase response rate, while having a more positive effect on the overall experience of the symposium. Evaluation should also be done with sponsors. During this project it proved to be very hard to get in touch with previous sponsors, but the one that was able to be reached indicated that some sort of evaluation would have been nice. I believe it would be easier to discuss things with them a couple of weeks after the symposium. Furthermore, INVITROM could benefit from evaluating their sponsorships, as it can help them improve their offers for the next year.

Use social media to promote activities and share content

Because social interactions are so important to INVITROM and its mission, I believe it is essential they use social media as a way to keep some interaction even when the annual symposium is still some time away. By actively using social media they can keep their audience posted on the developments of the symposium, but even more so the developments in the field of *in vitro* research. If the audience is looking forward to new updates on social media, they are also likely to look forward to the invitation for the new symposium, which will allow INVITROM to expand their current community.

Assign a board member to be responsible for marketing

During this project I helped out the organization by making some promotional material. (Appendix V) However, next year there will probably not be a student that can help them do so. I believe the organization could really benefit from having someone being responsible for marketing and communications. Considering the fact that she won an award at the last symposium for having the most interesting pitch, and that she has some experience using photo editing software such as adobe photoshop and illustrator, Gerian Prins would be very suited for this task. She can write and design promotional material for the next symposia, but also update some parts of the website, such as the mission statement and the standardized sponsorship page. By having someone in charge of marketing, there is more clarity as to how this will be made. It can always be improved upon by the entire board if they think this is necessary.

Consider neurobiology and oncology as content for the next symposium, but remain multidisciplinary

Considering both the developments in the scientific fields and the amount of products that are being developed in the fields of neurobiology and oncology, I believe these two topics are very suited to be part of INVITROM's program in the years to come. However, this does not mean that INVITROM should solely focus on these topics. One of the main unique selling points for INVITROM is that their symposium offers a wide variety of topics to be a part of the experience. If attendees wish to hear about solely neurobiology or oncology, other existing symposia are available. I believe the multidisciplinary program INVITROM offers is currently very unique, but also quite necessary with the rapid development of many multi-cellular *in vitro* models.

Think about the next step

This report mainly focusses on the annual symposium and finding new sponsors. These two aspects are a big part of keeping the organization up and running and the findings in this report could help INVITROM generate more money than they need to organize the annual symposium. INVITROM should remember that they are a non-profit organization and act as such: When they make a lot of money, they should invest this to work towards their mission. From the analyses we found that members are interested in more social interaction. This could be a social event, but also an extra meet-up at a relevant regulatory body, such as the EMA, which is conveniently moving to Amsterdam in March 2019, or an interesting company, such as Boehringer Ingelheim could be interesting for INVITROM to host for its members. By hosting such events, INVITROM can collaborate directly with the governing bodies as well as companies, while providing their members with additional interesting content and contact. These events could potentially interest their members anyway, and it could be of value to discuss ideas for these types of events with the members present at next year's symposium.

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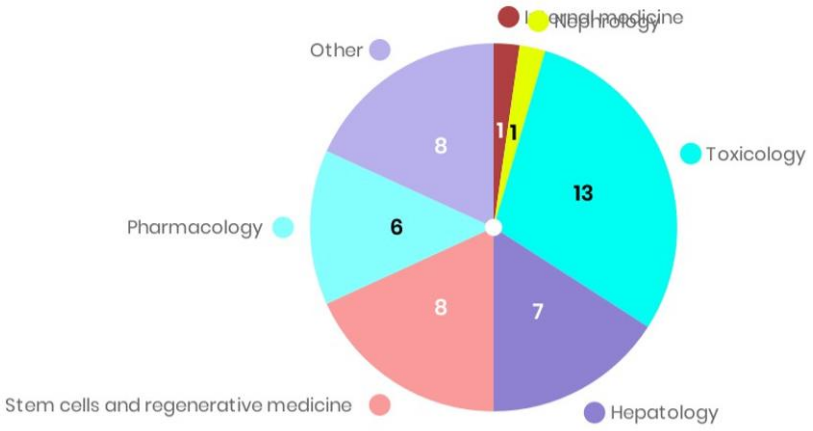
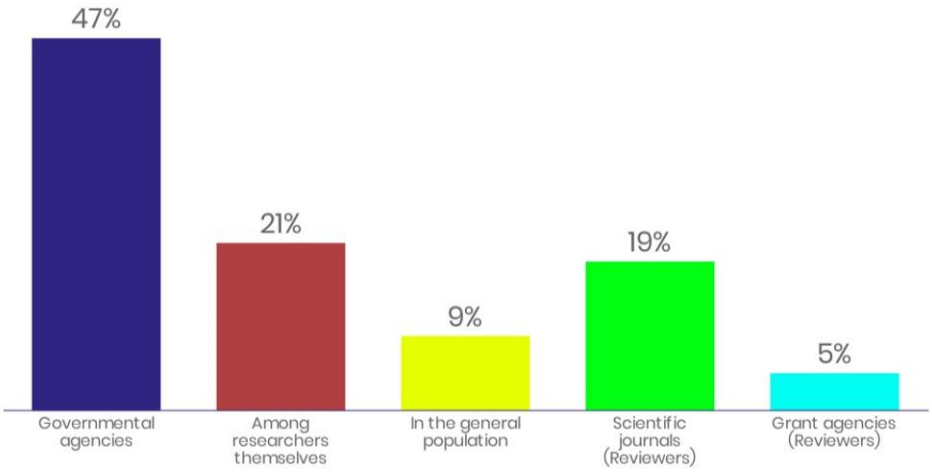
VII. Appendix

Appendix I – INVITROM Mendeley Survey results

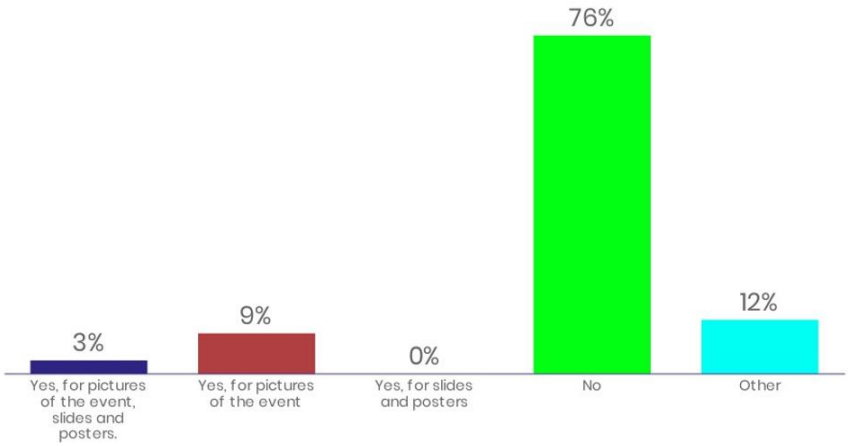
What field do you work in?



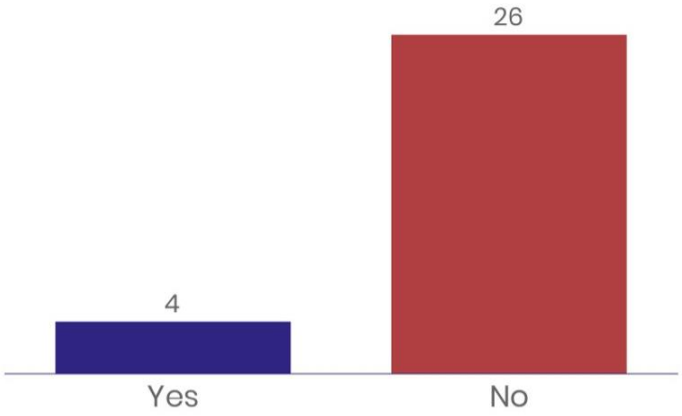
Where do you think acceptance of in vitro methods is most problematic within biomedical research?



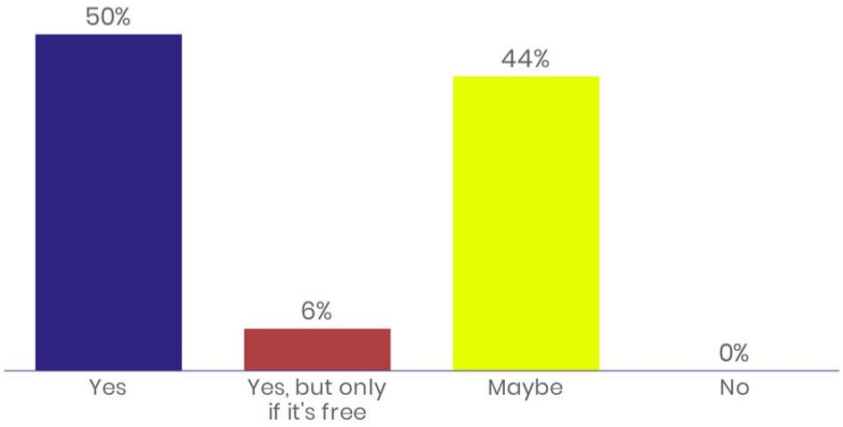
Do you ever visit the INVITROM website? And what for?



Do you think INVITROM events have stimulated you to form new collaborations?



Would you be interested in attending other events hosted by INVITROM?



Appendix II – INVITROM Financial statement 2017 and budget 2018

Financial statement of INVITROM
For fiscal year 2017 (1 January to 31 December 2017).

(All Amounts are in EUR)

	Banking account	Saving account	PayPal account	subtotal	TOTAL
REVENUES					
Membership fees	1655.00	-	590.00	2250.00	
Interest	-	36.48	-	36.48	
Sponsoring	750.00	-	-	750.00	
Transfer	1500.00	-	-	1500.00	
					4536.48
EXPENDITURES					
Cost of Banking	130.55	-	14.60	146.15	
Conference costs	3343.55	-	-	3343.55	
Sponsoring ESTIV	250.00	-	-	250.00	
Website	100.35	-	-	100.35	
Transfer	-	-500.00	-1000.00	1500.00	**5339.05**
NET INCOME 2017					**-802.57**

Declared certified copy, signed at Mol, Belgium on 14 June 2018

Peter Olinga
Chairman

An Van Rompay
Treasurer

1/2

Balance sheet - 2017 from INVITROM

ASSETS:		
• banking account	748.04	
• Saving account	21092.42	
• PayPal account	310.71	
TOTAL ASSETS		**22151.17**
LIABILITIES		
○ Opening balance (1 January 2017)		
○ Banking account	667.49	
○ Saving account	21555.94	
○ PayPal account	730,31	
○ Net income 2017	-802.57	
TOTAL EQUITY		**22151.17**

Declared certified copy, signed at Mol, Belgium on 14 June 2018

Peter Olinga
Chairman

An Van Rompay
Treasurer

Budget of INVITROM
For year 2018

(All Amounts are in EUR)

	Banking account	Saving account	PayPal account	subtotal	TOTAL
REVENUES					
Membership fees	1800.00	-	500.00	2300.00	
Interest	-	30	-	30.00	
Sponsoring	250.00	-	-	250.00	
Transfer	1000.00	-	-	1000.00	
					3580.00
EXPENDITURES					
Cost of Banking	135.00	-	20.00	155.00	
Conference costs	2025.00	-	-	2025.00	
Sponsoring ESTIV	250.00	-	-	250.00	
Website	150.00	-	-	150.00	
Transfer	-	1000.00	-	1000.00	**3580.00**
NET INCOME 2017					**0.00**

Declared certified copy, signed at Mol, Belgium on 14 June 2018

Peter Olinga
Chairman

An Van Rompay
Treasurer

1/1

Appendix III – Posters used during the annual symposium

Why do you attend the annual INVITROM symposium?

INVITROM
International Society for In Vitro Methods

promotion of
development, application and acceptance
of in vitro models in the biomedical research

Do you have any ideas for other events INVITROM could host?

INVITROM
International Society for In Vitro Methods
promotion of development, application and acceptance of in vitro models in the biomedical research

Do you have any suggestions for INVITROM or the annual symposium?

Website

Symposium

The organisation

Other

INVITROM
International Society for In Vitro Methods
promotion of development, application and acceptance of in vitro models in the biomedical research

Appendix IV – Personal communications with the KNAW

Beste Devi Seijkens,

Dank voor je e-mailbericht.

Het besluit tot het instellen van een nieuw Akademiefonds volgt op de evaluatie van een viertal oudere KNAW-fondsen, te weten Akademie Colloquia, Congressubsidiefonds, Fonds Bijeenkomsten KNAW-leden en Visiting Professors. Daaruit bleek dat genoemde programma's niet of nauwelijks meer aansluiten bij actueelKNAW-beleid of initiatieven vanuit de KNAW-domeinen. Bovendien is nu sprake van een versnipperde inzet van middelen, waarbij de 'opbrengsten' uit het mede-financieren van internationale bijeenkomsten en werkverblijf van buitenlandse onderzoekers in Nederland niet opwegen tegen de zeer hoge personele organisatiekosten. Genoemde fondsen zullen daarom in de loop van 2018 worden afgebouwd.

Eind maart is de KNAW-commissie van start gegaan die het KNAW-bestuur zal adviseren over doelbestemming(en) van een nieuw in te richten Akademiefonds.

De Commissie Akademiefonds zal met een voorstel komen voor het doelmatig en kosten-efficiënt inzetten van KNAW-middelen voor stimuleringsprogramma's die ambities ondersteunen zoals geformuleerd in de Strategische Agenda van de KNAW 2016-2020 en/of aansluiten bij activiteiten van de KNAW-domeinen.

Ik hoop je hiermee voldoende te hebben geïnformeerd.

Met vriendelijke groet,

Rachel Basaur

KNAW Wetenschapsfondsen

KONINKLIJKE NEDERLANDSE

AKADEMIE VAN WETENSCHAPPEN

Het Trippenhuis

Kloveniersburgwal 29

Postbus 19121

1000 GC Amsterdam

Telefoon 020 551 0804

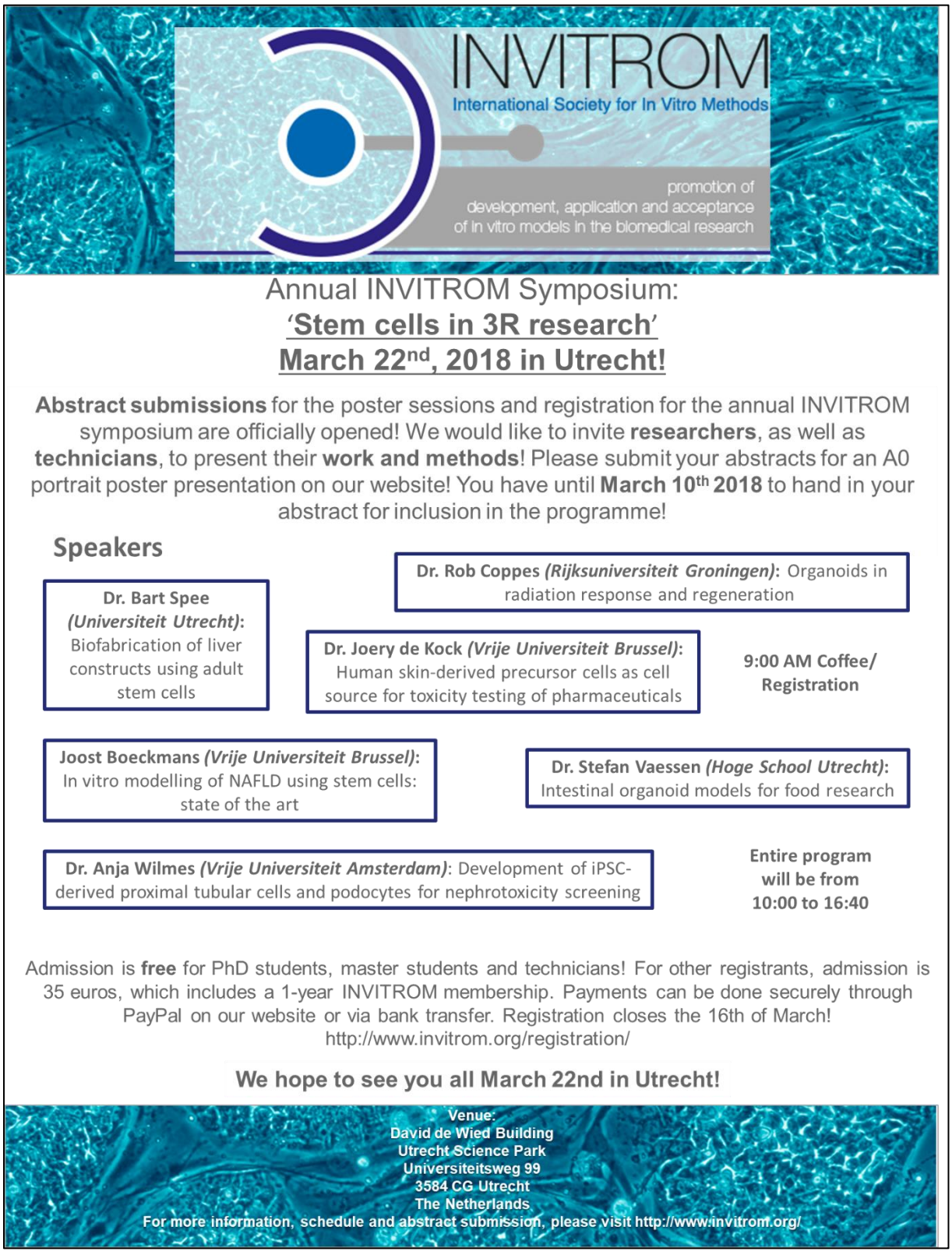
Fax 020 620 4941

www.knaw.nl

Aanwezig op maandag, dinsdag en donderdag.

www.knaw.nl/blijfopdehoogte

Appendix V – Promotional material made during this internship



Program and registration details for the annual INVITROM Symposium

'Stem cells in 3R research'

The international society for *in vitro* methods will once again host its annual INVITROM symposium on **March 22nd, 2018**

The location is:

David de Wied Building

Utrecht Science Park

Universiteitsweg 99, 3584 CG Utrecht The Netherlands

If you are not a PhD or Masters student, the admission is 35 euros, which includes a year INVITROM membership. Payments can be done safely through PayPal on our website or banktransfer Admission for technicians, PhD students and master students is **free**! Please register before the 16th of March here.

Abstract **submissions for the poster sessions and registration for the annual INVITROM symposium are officially opened! We would like to invite researchers, as well as technicians, to present their work and methods! Please submit your abstracts for an A0 portrait poster presentation** here**. You have until March 10th, 2018, to hand in your abstract for inclusion in the programme!**

Programme

9:00 Registration/coffee
10:00 Introduction by Peter Olinga
10:20 Dr. Bart Spee (Universiteit Utrecht): Biofabrication of liver constructs using adult stem cells
11:00 Dr. Joery de Kock (Vrije Universiteit Brussel): Human skin-derived precursor cells as cell source for toxicity testing of pharmaceuticals
11:40 Coffee/tea/posters
12:10 Joost Boeckmans (Vrije Universiteit Brussel): *In vitro* modelling of NAFLD using stem cells: state of the art
12:30 Young scientist speed presentations
13:10 General assembly *(open to all INVITROM members, 30 min.)*
13:10 Lunch/posters
14:10 Dr. Rob Coppes (Rijksuniversiteit Groningen): Organoids in radiation response and regeneration
14:50 Dr. Anja Wilmes (Vrije Universiteit Amsterdam): Using induced pluripotent stem cells to

study nephrotoxicity
15:30 Coffee/tea/posters
16:00 Dr. Raymond Pieters: Intestinal organoid models for food research
16:40 Drinks

We hope to see you all

March 22nd in Utrecht!