Cell Constraint et Cancer

Join Forces Against Cancer

Detailed document published on the occasion of the increase of capital of Cell Constraint & Cancer SA, Emission of 79,015 Warrants (Coupons Company Stock) to be exercised before December 31, 2018 at a unit price of € 20 (nominal € 5 + premium of € 15) for a total amount of € 1,580,300

R & D scheme and valuation of Cell Constraint and Cancer

	Proof of Concept in vitro		Proof of Concept in vivo		Presentation to the Scientific Community (Articles, Congress) of the In Vivo Proof of Concept	End of the ISF Public Funds Research	European Consortium contract with Stanford submission FETOpen and R21 (NCI)	Animal Experimentation of Proof of Efficacy	Presentation to the Scientific Community (Articles, Congress) of the In Vivo Proof of Efficacy on the pancreas	Preclinical Dossier Development Looking for an Industrial Partner		Phase I / IIa Human Demonstrator Arrival on the market	
	180 K€ invested		180 K€ invested			Need funding 250 K€							
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Estimated value of the company	75 K€		165 K€			910 K€			5 M€	5 M€	5 M€	25 M€	50 M€		500 M€
Value of the action (base 2017)	3.55 €		4.30 €			14.30 €			20 €			400 €	400 €		1 000 €

This subscription is open:

- to anyone who can assess the risks of such investment,
- the taxpayers of the French IRPP (who will receive a certificate allowing them to reduce their tax).

The shares are freely negotiable by mutual agreement.

On page 3 of this document, you will find subscription form to participate in this capital increase.

Warning

This information document is intended for persons interested in the purchase, sale and / or exercise of Warrants issued by the SA Cell Constraint & Cancer (CC & C).
They can only participate in this operation directly for their own account.
This document sets out the current situation, the future business development plan and the financial perspectives of CC & C SA.
This outlook is subject, of course, to the uncertainties inherent in the development of a business plan, Capital subscription is for investors capable of appreciating the risks.

The capital increase proposed here by CC & C SA is not part of a public offering of financial securities.

The preparation of this information document is therefore in no way mandatory and the 'Autorité des Marchés Financiers' (the AMF) does not have to be asked to give its opinion on this transaction, which is not part of the part of its mission.

However, CC & C SA has opted to prepare this document, for the sake of transparency, to deliver useful information to both its own shareholders and future investors, so that they can, knowingly, take the decision to enter the capital of the company. That is why this document is drawn up in the spirit of the headings usually imposed during AMF operations.

SUMMARY

Application form for the capital increase
by exercise of share subscription warrants
CELL CONSTRAINT & CANCER SA

SA capital : 395 075 € ■ RCS Tarascon 511 620 890 ■ Head office: 331, Chemin de la Poterie - Le Mas l'Hermite - 13280 Raphèle-Les-Arles, France

Characteristics of the issue of warrants (share subscription warrants) decided by the Board of Directors on December 31, 2017:

- ✓ Parity: the exercise of **a warrant allows to obtain 1 new action**
- ✓ Exercise price of the warrant: **20 €**
- ✓ Validity period of the warrant: **until December 31, 2018**

This transaction is intended to former shareholders as well as new shareholders able to assess the risks.

I suscribe as:

- ❒ Former Shareholder
- ❒ New Shareholder (Attach a photocopy of an ID card)

I, the undersigned, ☐ Mr ☐ Mrs ☐ Mr and Mrs ☐ Mr or Mrs

Last Name _____ First Name _____

Born the __ __ __ __ __ __ __ __ in _____

Address _____

Zip Code __ __ __ __ __ City _____ Country _____

Tel. _____ Email _____

I declare to subscribe to _____ shares Cell Constraint & Cancer SA.

Each warrant to be exercised at the price of 20 € allows automatically to obtain 1 new share.

In support of my subscription, I enclose a payment in the amount of _____ € representing the total of my contribution.

Payment method:

- ☐ Online payment CB or Paypal (see CC & C website)
- ☐ Check payable to Cell Constraint & Cancer
- ☐ Bank Transfer

In case of payment by Bank transfer:

The payment of your subscription must be attached to this bulletin and addressed to the head office of Cell Constraint & Cancer SA: 331, Chemin de la Poterie – le Mas l'Hermite - 13280 Raphèle-Les-Arles, France
The regulations for all subscriptions are deposited in the CELL CONSTRAINT & CANCER SA account at LCL Bank, 16, rue du Président Wilson ■ 13200 Arles, France
Bank code 30002 ■ Code Counter 03332 ■ Account ID 0000072048 S ■ Key 18 ■ Domiciliation: CL Arles (03332)
IBAN: FR19 3000 2033 3200 0007 2048 S18 ■ Code B.I.C: CRLYFRPP

- ✓ I agree to subscribe this day, in the absence of any bank or financial solicitation, as defined in Article 341-1 of the Monetary and Financial Code (France).

In _____

On __ __ __ __ __ __ __ __

SIGNATURE preceded by the mention:
« Good for subscription to "number" shares »

The word from the president of Cell Constraint & Cancer SA

Raphèle-les-Arles, April 4, 2018

Cell Constraint & Cancer SA develops a patented process for treating cancer using purely physical means - mechanical signals - and not biological: in other words, it is not a drug, a molecule or an immunological treatment

This breakthrough innovation is an application of a new approach to cancer, the "Physical Oncology". This is the study of cancer with the mathematical and experimental tools of physics and the use of mechanical signals to act on cancer.

Our patent protects the possibility of applying "a stress field" (Which can be approximated without going into details to a set of forces and pressures) to a tissue in vivo. It consists in positioning magnetizable nanoparticles around tumors and then apply a magnetic field gradient to the tumor / nanoparticle assembly, from the outside. Nanoparticles then behave like BioActuators transforming magnetic energy into mechanical energy. This results in a stress applied to the tumor. We have known for more than 10 years that pressure applied to a tumor in vitro leads to a return to normal of cancer tissue (M Paszek 2005). In the article princeps of M. Paszek et al, it is shown that we can turn into cancerous a culture of normal breast cells in three dimensions (3D), and vice versa. Since then, other authors have confirmed the action of mechanical signals. Our innovation concerns the transition from in vitro 3D to in vivo, that is to say from "test tube" to the animal.

The goal is to propose a treatment for pancreatic cancer, our first indication.

RESULTS OF RESEARCH OBTAINED DUE TO FUNDS RAISED SINCE 2009

Near € 650,000 has been collected since 2009 from individuals to obtain our **Proof of Concept in vivo** published in 2016. It involved comparing a treated group of mice, that is to say with nanoparticles and magnetic field gradient with three control groups. We analyzed the results with Dr. JM Guinebretière (Institute Curie, Paris)**: the concept is validated.** There is a significant difference between the treated group and the control groups. This difference relates to the increase in tumor volume measured in vivo which is very significantly decreased ($p = 0.015$) in the treated group compared to the 3 control groups (with particles and without gradient, with gradient and without particles, without gradient or particles). There is also a significant difference in favor of the treated group when measuring the surface of the living tumor, ex vivo, on digitized histological sections ($p < 0.05$).

An article presenting these results was published on April 21, 2016 by the journal PloS One by R Brossel et al.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0152885

This article has just over 3,500 readers.

A presentation was made in June 2016 in Boston at the AACR conference and published in Cancer Research

http://cancerres.aacrjournals.org/content/77/2_Supplement/A41.short

FURTHER RESEARCH

The second and final stage of research: **Proof of Efficacy**: "**Action of a stress field on human pancreatic cancer grafted in mouse pancreas**".

This type of (orthotopic) transplant is one of the best animal models of human disease. This **Proof of Efficacy** in the animal supposes to manufacture two medical devices:

1 / **A magnetic field gradient generator** ("generator"). It is an electromagnet capable of generating an active gradient about 3 cm deep, in the middle of the abdomen of a mouse.

2 / **NanoParticles** (NP) of iron oxide, vectorized, injectable IntraVenously (IV) which will be targeted on molecules (integrins alpha v beta 3 [IAVB3]) overexpressed in neovessels surrounding the tumor.

OUR BUSINESS MODEL

Until the end of 2017, it was based on the shareholders.

We are now led to seek public funds. At the same time, we will be soliciting our shareholders in the coming months and will seek new ones in the form of a fund raising of €250,000. This sum is necessary to pass the European (H2020) and French financial stress tests.

Public funds sought:

1 / in Europe, setting up a grant file "Fet Open" (H2020).

2 / in the USA, submitted to the National Cancer Institute, in collaboration with Stanford University.

THE PRODUCT FOR THE PATIENT

We already mentioned the two medical devices:

1 / The generator will no longer be an electromagnet like in animals, but a more powerful superconducting magnet to reach up to 10 cm deep. The technology of superconductors is well controlled (MRI, particle accelerators...) but more complex and expensive. That is why we will seek, from the beginning of the development, a partnership with a medical imaging manufacturer.

2 / NPs vectorized to IAVB3 will be pharmaceutical grade, IV injectable in the patient.

We have, so far, not enough information to determine whether it is a single injection or repeated.

The FET Open file provides a comparison between vectorized liposomes and encapsulating iron, and iron NPs directly vectorized on their surface.

AFTER THE RESEARCH WILL COME THE DEVELOPMENT

which will require the arrival of investors then industrial partners. The arrival on the market is expected in 2023.

TODAY WE NEED TO INFORM

Physical Oncology has received little attention so far and was reserved for a small academic circle.
In the US, the National Cancer Institute has, in 2009, granted the 12 best universities in the United States to bring cancer physicians and bioengineers together in a "Office for Physical Sciences and Oncology".

In Singapore, an Institute of Mechanobiology hosts several hundred researchers dedicated to this new approach to oncology.

In Europe, there are some scattered academic laboratories (France, Germany, Spain...).

Apparition of Physical Oncology in Wikipedia https://en.wikipedia.org/wiki/Physical_oncology
But the pedagogical effort is advancing:
- TED Conference by Mina Bissell - https://www.ted.com/speakers/mina_bissell
- Article by Erika Jonietz in Nature - http://www.nature.com/naturejobs/science/articles/10.1038/491S56a
- Our article in PloS One of April 21, 2016 - http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0152885

THE SCIENTIFIC ENVIRONMENT

Two European programs have recently been approved that demonstrate the rise of physical oncology.

1 / Imaging the Forces of Cancer (H2020)

This aims to measure the "Stress Tensor" of a liver tumor using IRM elastography.
The Stress Tensor can be seen as a generalization of the notion of Stress Field
A single mathematical entity can therefore summarize all the constraints of a tumor.
This program is only intended to give a picture of the stresses in the tumor, and this has already been published in the breast cancer cases, but it may offer a therapeutic purpose to Physical Oncology: restore the nominal value of the tumor stress tensor.

2 / "Magneton" (FET Open 2017)

In this project, magnetic "Nano Bioactuators", externally controlled, are brought to stem cells in the brain to control their differentiation. The concept of Actuator, in this project, is very close to ours.

OUR OBJECTIVE:

TO MAKE AVAILABLE A NEW TREATMENT OF PANCREAS CANCER IN 2023, THEN DEVELOP NEW INDICATIONS: BRAIN CANCER, LIVER…

A DECISIVE STEP

Remember that this is not a molecule, a drug-like product or immunological or cellular, but the combination of two medical devices and the use of the laws of physics. So, there is only 3 to 4 years of development before the arrival to the market. Furthermore, toxicity (major cause of molecules arrest of development) is known and a priori minimal.
Moreover, this process is based on the laws of physics: the results obtained, and future, can be modeled and are therefore predictive, further reducing the hazard related to biology.

The subscription price is €20 per action. The premium has been increased after obtaining our In Vivo Proof of Concept, which shows that the basic principles of this innovation work in the experimental setup in vivo. It remains now to obtain the Proof of Efficiency, a positive result of this method of treating cancerous tumors in an environment close to that of a human disease, **the Pancreatic Cancer**. This is the purpose of this fundraising. The premium should increase sharply after obtaining the Proof of Efficacy.

BEYOND CANCER PANCREATIC

This type of treatment could be applied to all so-called locally advanced cancers (locally advanced) and without a suitable therapeutic solution to date, such as brain cancer (glioblastoma) or primary cancer of the liver and more broadly to all cancers provided with a network of peri-tumoral vessels and put in a magnetic field gradient.

Barthélémy BROSSEL,
CEO of Cell Constraint & Cancer SA

Chapter 1

Responsible for the Subscription Call Document, of Audit and Information

1.1 PERSON IN CHARGE OF THE SUBSCRIPTION DOCUMENT

Mr. Barthélémy BROSSEL, CEO
10, bd Louis Salvator
F13 006 Marseille, France

To join us:
Phone: +33 (0) 6 738 769 87
Email: brossel.remy@gmail.com
Website: www.cellconstraintcancer.com
Address: le mas l'Hermite, 331 chemin de la Poterie - F 13280 Raphèle-les-Arles, France

Press relations
Barthélémy BROSSEL
Phone: +33 (0) 6 50 22 79 64
Email: barth.brossel@gmail.com

Shareholder & Investor Relations
Christine GRAU Tel: +33 (0) 4 901 848 50
Email: investors@cellconstraintcancer.com

1.2 CERTIFICATION OF THE PERSON IN CHARGE OF THE SUBSCRIPTION DOCUMENT

" To my knowledge, the data in this subscription call document are true, they include all the information necessary for investors to base their judgment on the assets, business, financial situation, results and prospects of the company CC & C SA, as well as the rights attached to the proposed securities. They do not include an omission of such a nature as to alter its scope"

Made in Raphèle-les-Arles, April 4, 2018

Barthélémy BROSSEL,
CEO of CC & C SA

1.3 ACCOUNT CONTROL OFFICERS

Statutory Auditor:
Mr. Eric MOYA, 4, rue Jules Ferry, 13200 ARLES, France (registered at the Court of Appeal of Aix-en-Provence)
Appointed in the articles of association for a period of six fiscal years, ie until the Ordinary General Shareholders Meeting which will be called to approve the financial statements for the year ended December 31, 2020.

Supply external auditor:
Mrs. Marielle BONNEIL 565, rue Marcellin Berthelot, 13090 AIX-EN-PROVENCE, France (registered at the Court of Appeal of Aix-en-Provence).
Named in the statutes for a period of six years, ie until the Annual General Meeting called to approve the financial statements for the year ended December 31, 2020.

Chapter 2

Issue of Shares

2.1 PURPOSE OF ISSUE

The capital raised through this capital increase will be used to fund the activities of research and Development of CC & C SA.

Research:

- Progressive hiring of employees including 2 researchers and a Product Manager;
- Feasibility studies in electrotechnics and nanoparticles; the study of Proof of Efficacy in vivo in the rodent; the construction of an animal demonstrator;
- Concurrent patent taking, accompanying the development.

Development:

Additional funds will then be needed to:

- CE Marking;
- "Preclinical" file on the animal preceding the introduction in humans, in a phase I / IIa;
- Construction of a prototype for human use;
- " Fast Track " procedure giving access to the market after this phase I / II.

We estimate at K€ 250 the cost of research; to M€ 2 the marking and the preclinical study; to M€ 3 the cost of arrival at the market, including the clinical study.

2.1.1 Authorization to carry out this capital increase operation

The General Meeting of Shareholders of CC & C SA of June 3, 2016, authorized the Board of Directors to increase the share capital on one or more occasions if it deems necessary, up to a maximum of €5 million, until December 31, 2018.

At its meeting on December 31, 2017, the Board of Directors decided, within the framework of the authorization described above:

- the issuance of 79,015 share warrants (BSA) awarded to all shareholders (ie good given for every share held);
- that the granted BSAs each give the right to subscribe for one **new share at a unit price of € 20.** (Nominal €5 plus an issue premium of € 15);
- And this until December 31, 2018.

In accordance with the provisions of Article L. 225-132 paragraph 5 of the French Commercial Code and the decision of the Board of Directors, the exercise of the Warrants automatically entails the waiver by the shareholders of the Company issuing the new equity securities of the Company, their preferential subscription right relating to said securities.

2.1.2 Existence of 103 400 stock warrants for founding shareholders

At the Extraordinary Shareholders Meeting of CC & C SA of May 25, 2009, 16 Warrants (BSA) were granted to each of the 1,850 original shares of the founders, ie 29,600 BSA.
750 were utilized by Rémy Brossel on September 29, 2016 for a capital increase.
The Shareholders Meeting of May 22, 2017 voted to change the allocation of Founding Share Subscription Warrants to 103 400 BSA at € 5 and extend their validity until April 30, 2020.

2.2 INFORMATION RELATING TO THE PROPOSED TITLES

2.2.1 Nature of the proposed titles

79 015 B SA (stock warrants) gives the right to subscribe for 1 new share at a price of € 20. These shares will be immediately assimilated to the already existing shares, will have to be fully paid up during the present subscription and will be exercised on their date of creation.

2.2.2 Exercise price of the warrants

The exercise price of the warrants is €20, giving entitlement to 1 new action. The shares will be fully paid up at the time of subscription. No fee will be charged to the subscriber (No brokerage, no management fees, no custody fees).
The subscription of the new shares through the exercise of the warrants will be made in cash and will be fully paid up at the time of subscription.
The new shares will be subject to all statutory provisions and will enjoy the specific rights reserved for them.

2.2.3 Value of the Shares

The nominal value is € 5 and the issue premium at €15.

2.2.4 Amount of issue

The amount of the issue is €1,580,300 including €395,075 in nominal value and €1,185,225 in issue premium.
This operation is divided into 79,015 shares.

2.2.5 Subscription period

The warrants are exercisable until 31 December 2018.
These warrants will become obsolete and will lose any value after December 31st, 2018.

2.2.6 Domiciliary institution (where subscriptions are received)

Subscriptions on behalf of CC & C S A, are received without charge, at the registered office:
Le mas l'Hermite, 331, Chemin de la Poterie 13280 Raphèle-les-Arles, France

Checks in support of the subscription must be in the name of "CC & C SA".
They will be deposited with Banque LCL, agency 03332 (16, rue du Président Wilson - 13200 Arles, France)
Bank code 30002 - Counter Code 03332 - Account Number 0000072048 S - Key 18

For transfers from abroad, the international bank account identifier (IBAN = International Bank Account Number): FR13 300 2033 3200 0007 2048 S18

2.2.7 Procedures for issuing titles

The shares will benefit from their creation and will be assimilated to existing shares. They will be subject to all the provisions of the statutes. The shares are in registered form in accordance with the provisions of article 94 - 01 of the law of December 30, 1981 and the decree of May 2, 1983. They can be deposited in account (in "pure nominative", without expenses) directly to the company, or domiciled in a financial institution (in "administered registered", provided custody fees) at the option of the subscriber.

2.2.8 The register of shareholders

The register of shareholders is held by Cell Constraint and Cancer.

2.2.9 Methods of returning the funds in the event of non-realization of the operation

Not applicable in the case of exercise of warrants.

2.2.10 Performance guarantee

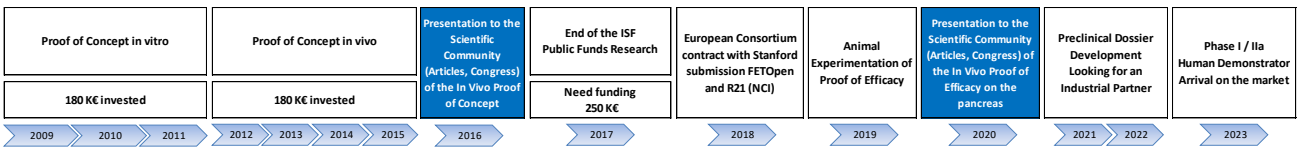
There is no guarantee of a 'good end' for the entire operation.

2.3 SUBSCRIPTION PRICE OF THE SHARES AND ELEMENTS OF APPRECIATION

The CC & C SA share is offered at a unit price of €20.

2.3.1. Estimate of the value of the action Cell Constraint & Cancer SA

R & D scheme and valuation of Cell Constraint and Cancer



Estimated value of the company	75 K€		165 K€			910 K€		5 M€	5 M€	5 M€	25 M€	50 M€	500 M€
Value of the action (base 2017)	3.55 €		4.30 €			14.30 €		20 €			400 €	400 €	1 000 €

- Companies that target markets with significant potential (such as cancer treatment) give hope **for very important capital gains if successful**.
- But, and this is the other side of the coin, the sometimes high failure rate of these companies makes it **a risky investment**.
  Nevertheless, a cancer treatment **based on the laws of physics and not the biological laws** is a guarantee of robust results and a greater probability of success later.

Recall here that Article 73 of the French law on commercial companies protects the shareholders who cannot in any way support the losses of a public limited company beyond the amount of their subscriptions deducted from their benefit of the tax reduction.

2.4 GENERAL INFORMATION ON ISSUED SECURITIES

2.4.1 Rights attached to issued shares

The 79,015 shares issued will all be treated as the 79,015 shares already constituting the capital of CC & C SA which are all of the same rank and give the same rights in the distribution of both profits and bonus in the event of liquidation.
Each share also gives the right to vote and representativeness in general meetings, as well as the right to be informed about the progress of the company and to obtain certain social documents at the times and under the conditions provided by law and the statutes.
Each share of the Company is entitled to dividends. Dividends represent the share of profits or reserves that the ordinary general meeting, at its annual meeting, decides to distribute to the shareholders after allocation, if necessary, of the legal reserve (5% of the profits made). In the event of the liquidation of the company and the existence of a liquidation bonus, it would then be distributed among the shareholders in proportion to their share of the share capital, subject to the creation of priority shares.
The title of the shares being registered, the dividends that could be paid are sent individually. Dividends not received by their beneficiaries within five years are then paid to the French State.

NB: CC & C SA does not provide dividend distribution until the company is profitable.

2.4.2 Accreditation clause

There is no approval clause. CC & C SA shares are freely transferable.

2.4.3 Registration in securities account (registered securities service)

The shares must be registered in registered form in the name of the shareholders at the registered office of the Company.

2.4.4 Profit from tax reductions for the benefit of the subscribers of this transaction

► The French law of 21 August 2007 (Law n ° 2007-1223) provides for a tax advantage of 18% on the French IRPP. The cost price is therefore 16.4 €.

The shares must be kept for 5 years, except refund of the tax reduction.

2.4.5 Tax regime of the shares

The tax regime of the Company's shares in the current state of French law is described below. However, it is pointed out that this information is only a summary of the applicable tax regime and that their particular situation must be studied with their usual tax advisor.

2.4.5.1 Shareholders tax resident of France

a) individuals holding shares in their private assets

1) Income from a possible dividend

CC & C SA does not plan to distribute dividends until the company is profitable.

2) Capital gains (Article 150-0 A of the General Tax Code)

Pursuant to Article 150-0 A of the French Tax Code, capital gains from the sale of CELL CONSTRAINT & CANCER shares or preferential subscription rights by natural persons are subject, from the first euro, to the tax on income at a progressive rate.

The surplus value is also subject:
- the one-off flat-rate levy (UTP) at a rate of 12.8% in 2018;
- to French social security contributions at the rate of 17.2 % in 2018.

In accordance with the provisions of Article 150-0 D 11 ° of the French General Tax Code, any capital losses that may have been realized in a year may be offset against capital gains of the same nature realized in the same year or in the following ten years.

3) Special scheme for Stock Savings Plan

CC & C SA shares may be subscribed and held in the context of a 'PEA'. Under certain conditions, the PEA is entitled to an exemption from income tax for the products and the capital gains of the securities contained therein. **The benefit of the tax reduction described in 2.4.4 cannot be combined with the PEA**.

NB: The subscription order must come from the institution that manages the PEA.

b) Shareholders, legal entities subject to corporate income tax

1) Dividends

The company intends to reinvest its results first and foremost in order to fully favor growth.

2) Capital gains

Capital gains realized on the sale of the portfolio securities are, in principle, included in the profit or loss subject to corporate income tax at the normal rate of 33.33 % (or, where applicable, at the tax rate of 15 % within the limit of € 38,120 per twelve-month period for companies fulfilling the conditions laid down in Article 219 I-b referred to above), increased, where applicable, by the social contribution of the conditions mentioned above.

2.4.5.2 Shareholders non-resident of France

1) Dividends

CC & C SA does not provide for the distribution of dividends until the company is profitable.

2) Capital gains

The taxation provided for in Article 92B of the French General Tax Code does not apply to capital gains realized by persons whose tax domicile or registered office is not located in France within the meaning of Article 4 -B of the General Tax Code on the sale of securities for valuable consideration.

2.4.6 Trading place

CC & C SA shares are not tradable on any regulated share market.

2.4.7 Competent courts

The competent courts, in the event of litigation, are those of the registered office of the Company, when the Company is defendant and are designated according to the nature of the disputes except contrary provisions of the French new code of civil procedure.

Chapter 3

GENERAL INFORMATION ABOUT CC & C SA AND ITS CAPITAL

3.1 GENERAL INFORMATION ABOUT CC & C SA

3.1.1 Name and registered office

The company's name: **CELL CONSTRAINT & CANCER SA**
The head office: Le Mas l'Hermite 331 Chemin de la Poterie - F 13280 Raphèle-les-Arles, France
The offices: Les bureaux de Fourchon - 15, rue Charlie Chaplin - 13200 Arles, France
Telephone: +33 (0) 6 738 7 69 87 - E-mail: cellconst@gmail.com
Website: www.cellconstraintcancer.com

3.1.2 Legal form of the company and duration

CELL CONSTRAINT & CANCER SA is a French limited company with a capital of € 395,075, governed by the legal and regulatory provisions in force.
The articles of association of CELL CONSTRAINT & CANCER SA have been filed with the registry of the Commercial Court of Tarascon (13).
CELL CONSTRAINT & CANCER SA is owned by individuals.
Its life is set at 99 years, dating from its registration in the Trade and Companies Register, an expiry scheduled for 2108. It may be extended.

3.1.3 Social object

The Company's purpose is the research and development of innovative processes, based on the application of stress fields to cells or tissues, and the development of all innovative processes applied to biology and therapeutics, and more generally all financial or real estate transactions that may be directly or indirectly related to the corporate purpose or to all similar, related or complementary purposes.

3.1.4 Commercial Register

The company CELL CONSTRAINT & CANCER SA is registered in the Trade and Companies Registry of Tarascon under the number RCS Tarascon 511 620 890
Date of constitution: March 13, 2009
SIRET number: 51162089000026
APE code: 7120B

3.1.5 Social exercise

The company's financial year begins on January 1 and ends on December 31 of each year. It is for a period of 12 months.

3.1.6 Specific statutory clauses

3.1.6.1 Distribution of benefits

The allocation and distribution of profits obeys the rules laid down by law. There is no statutory reserve unless decided otherwise by ordinary general meeting.

3.1.6.2 General meetings

Shareholders are convened and deliberate under the conditions provided by law. It is specified that no minimum threshold of action is provided to open the right to attend general meetings. You must have at least one share to be considered as shareholder of the company.

3.1.6.3 Minority Protection

The company status provide that if the majority of shares are to be sold and change ownership, whether directly or indirectly (possibly through the transfer of ownership of a holding company of shareholders holding, directly or indirectly, the majority of "the company"), it will be obligatorily implemented by the prospective purchaser the guarantee for the benefit of the minority shareholders to be able to sell at the same price as the sale price of the majority block.
Information by letter would be sent to shareholders.

3.1.6.4 Difficulties and collective procedure

In the event of an alert on any fact likely to compromise the continuity of operations provided for in Article L. 225-232 of the French Commercial Code, the Board of Directors will meet to deliberate and inform the shareholders.
In no event shall a decision to file a declaration of cessation of payments with the Registry of the Commercial Court or the Commercial Court of First Instance in whose jurisdiction the company's registered office is located shall be taken without having first convened and meeting of the General Assembly.
If necessary, complete information on the accounting, financial and commercial situation on the origin of the difficulties and the forecasts of the company will be communicated to the shareholders.
If the General Meeting finds that the company is unable to meet the liabilities payable with its available assets, it will deliberate on the decisions to be taken, on the possible opportunity to carry out a capital increase and on the one to deposit a declaration of cessation of payments.

In the event of the foreseeable opening of a collective procedure, or after its opening, and to the extent that a continuation plan is considered conceivable by the shareholders against the opinion of the directors, they may ask to be discharged at least during the recovery period.

In any case, the General Meeting will appoint a person, whether a shareholder or not, to accompany the Chairman of the Board of Directors to the Board of Directors and present the resolution voted by the shareholders.

In case of opening of a period of judicial observation, the General Assembly will be immediately convened by all the existing means or by the judicial administrator if it has been appointed one.
The agenda of this Shareholders' Meeting will be, in addition to the approval of the financial statements for the last financial year, to present the current and future accounting, financial and commercial situation of the company, to proceed with a call for applications from the shareholders for strengthen the board of directors, study and present the feasibility of any form of recovery plan by way of continuation and propose a capital increase if necessary to ensure the recovery of the company.

In the event of a transfer plan, or in the event of judicial liquidation, in accordance with the provisions of article 1844-8 paragraph 2 of the Civil Code, the chairman of the board of directors in office or, as the case may be, any other person who has elected for this purpose at a General Meeting prior to the day of the pronouncement of the liquidation decision, will immediately be appointed liquidator "amicable" or "member" to exercise the rights of the company provided for in Articles L. 237 -19 and R. 237-12 of the French Commercial Code.

3.2 GENERAL INFORMATION CONCERNING CAPITAL

3.2.1 Share capital

The share capital amounts to three hundred and ninety-five thousand and seventy-five euros (€ 395,075) divided into seventy-nine thousand and fifteen (79,015) shares with a par value of five euros (€ 5 each) nominal, fully paid up. There are 87 shareholders.
All actions are of the same category.

3.2.2 History of capital since the creation of the company

Dated	Nature of the operation	No. of shares issued	Nominal amount of the capital increase	Premium	New capital	Cumulative number of shares	Nominal value of the action
13/03/2009	Formation of the SA by contribution in cash	1,850	€ 37,000	-	€ 37,000	1,850	€ 20
31/12/2009	Capital increase through BSA exercise	1,144	€ 22,880	€ 5,720	€ 59,880	2,994	€ 20
31/12/2010	Capital increase through BSA exercise	1,392	€ 27,840	€ 6,960	€ 87,720	4,386	€ 20
31/12/2011	Capital increase through BSA exercise	1,128	€ 22,560	€ 11,280	€ 110,280	5,514	€ 20
31/12/2012	Capital increase through BSA exercise	2,741	€ 54,820	€ 27,410	€ 165,100	8,255	€ 20
31/12/2013	Capital increase through BSA exercise	700	€ 14,000	€ 56,000	€ 179,100	8,955	€ 20
31/12/2014	Capital increase through BSA exercise	142	€ 2,840	€ 11,360	€ 181,940	9,097	€ 20

31/12/2015	Capital increase through BSA exercise	379	€ 7,580	€ 30,320	€ 189,520	9,476	€ 20
06/03/2016	Increase in capital By incorporation of the share premium account	-	€ 142	-	€ 331,660	9,476	€ 35
06/03/2016	Division of the nominal	56,856	-	-	€ 331,660	66,332	€ 5
31/12/2016	Increase in capital by exercise of BSA	10,273	€ 51,365	€ 67,535	€ 383,025	76,605	€ 5
31/12/2017	Increase in capital by exercise of BSA	3,075	€ 15,375	€ 46,125	€ 398,400	79,680	€ 5
	Cancellation of bonus shares in 2016 (decided in the GA of 22/05/2017)	-665	-3,325	-9,975			
		2,410	€ 12,050	€ 36,150	€ 395,075	79,015	€ 5

3.2.3 Potential capital

After this issue of warrants, if all the warrants are exercised, the capital would be increased by € 395,075 (79,015 shares of € 5 each).

3.2.4 Authorized and non-issued capital

The General Meeting of June 3, 2016 gave permission to the Board of Directors to increase capital by any means to the amount of five million euros, until 31 December 2018.

3.2.5 Shareholders' agreement

There is no shareholders' pact.

3.3 CONSEQUENCE OF THE EXERCISE OF THE WARRANTS

103,400 share subscription warrants were attributed to the founders at a price of 5 €.
All the rights described above will have the effect of increasing the capital of the total amount of rights actually exercised. In the event that all the warrants are exercised, the amount of the capital of CC & C SA would be increased to 1,307,150 € (taking into account this capital increase).

3.3.1 Summary table of warrants that have been issued by " CC & C SA"

Decision giving the authorization	Date of issue goods	Number of issued bonds	beneficiaries issued bonds	Exercise price	Number stock to emit	Dated expiration goods
Assembly of May 25, 2009 of May 24, 2012	May 25, 2009	29,600	Founding shareholders	€ 20	207,200	April 30, 2017
Assembly of May 22, 2017	Extension of voucher exercise	103,400 (instead of 29,600)	Founding shareholders	€ 5	103,400	April 30, 2020 (A u instead of 2017)
Board of Directors of December 31, 2015 & AGE of June 3, 2016	December 31, 2015	9,476	New and former shareholders	€ 100	66,332	December 31, 2016
Board of Directors Meeting of December 31, 2016	December 31, 2016	47,380	New and former shareholders	€ 20	47,380	December 31, 2017
Board of Directors Meeting of December 31, 2017	December 31, 2017	79,015	New and former shareholders	€ 20	79,015	December 31, 2018

3.4 NON-REPRESENTATIVE OF CAPITAL UNITS SECURITIES

Securities without capital are not allowed.

3.5 BREAKDOWN OF CAPITAL AND VOTING RIGHTS

Breakdown of capital and voting rights in April 2018

Shareholding before this capital increase	Number of shares or voting rights	% of the capital or voting rights
Rémy BROSSEL	9,083	11.50 %
Sylvie BROSSEL	6,454	8.17 %
85 individual shareholders	63,478	80.3 %
TOTAL	**79,015**	**100.00%**

Share capital and voting rights after completion of this capital increase, in the event of the exercise of all the 79,015 Warrants

Shareholding after this capital increase	Number of shares or voting rights	% of the capital or voting rights
Rémy BROSSEL	9,083	5.75 %
Sylvie BROSSEL	6,454	4.08 %
Individual shareholders	63,478	40.17%
New shareholders	79,015	50.00 %
TOTAL	**158,030**	**100.00%**

Share capital and voting rights as of December 31, 2017 in the event of the exercise of all the Warrants attached to the shares of the founders

Shareholding after exercise of all warrants attached to the original shares	Number of shares or voting rights	% of the capital or voting rights
Rémy BROSSEL	60,783	23.25%
Sylvie BROSSEL	58,154	22.24%
Individual shareholders	63,478	24.28%
New shareholders	79,015	30.23%
TOTAL	**261,430**	**100.00%**

3.6 GROUP MEMBERSHIP

CC & C SA is independent and does not belong to any group.

3.7 EXISTENCE OF A PARENT COMPANY OR A SUBSIDIARY

None.

Chapter 4

INFORMATION ON THE ACTIVITIES OF CELL CONSTRAINT & CANCER SA

4.1 PRESENTATION OF THE COMPANY AND ITS LEADERS

4.1.1. History

The project presented is the result of two years of reflections (2004 to 2006) of an informal working group, composed of a project leader, Rémy Brossel, Medical Oncologist and Physicist, of Pr. Stéphane Regnier, Robotics Laboratory, University of Paris VI, and Dr. Serge Fichelson, Hospital Practitioner, Claude Bernard Institute, Cochin Hospital. The purpose was to "biologize" an Atomic Force Microscope in order to measure the mechanical properties of cells in culture. Since the first tests were positive, the reflection turned towards a broader vision of the "constraint field" / cell interaction, or in practice between forces or pressures applied to cells or tissues, and these cells or tissues.

Tissue is defined as a set of similar cells (eg, liver tissue is composed of liver cells, the liver itself is a larger set (organ), with different tissues, nerves, vessels, and c.). Similarly, a cancerous tumor must be considered as an organ with two tissues: the tumor tissue itself and the ExtraCellular Matrix (ECM) that surrounds it.

Rémy Brossel then decided to go further and file a patent. This PCT patent WO 2015/004285 protects the invention in Europe, Japan and the US and was sold on 31 December 2016 for 1 euro to the company Cell Constraint & Cancer SA and valued 353 193 €.

The protected innovation can be summarized as follows: Magnetic particles are incorporated into the neoangiogenesis network that surrounds the tumor. A magnetic field gradient is imposed on the whole tumor and neovessels containing the particles. Nanoparticles act as bioactuators, transforming magnetic energy into mechanical energy. Each particle generates a force directed in the direction of the field and the set of particles generates a force applied to the cells of the tumor. It is widely proven that a force applied to cells or tissue modifies their qualities, or "phenotype": One can thus vary the growth of the cells (their multiplication), their differentiation (their degree of maturation), their programmed death (we speak of "apoptosis"), their necrosis and their possibility to migrate (very linked in oncology the possibility for a tumor to cause "metastases" that is to say tumors at a distance, so a breast cancer will become dangerous when there will be metastases, that is to say cancerous tissue of the breast tumor, in the liver, brain, bones, etc.).

These five variables (growth, differentiation, apoptosis, necrosis and migration) are summarized under the vocable "phenotype". One should add "cellular architecture" to switch from cell phenotype to tissue phenotype. Mina Bissell says: "In oncology, the tissue phenotype is dominant over the cellular phenotype".

Creation of Cell Constraint & Cancer SA (CC & C):

The company has been in existence since March 13, 2009. The articles of association were drafted by Maître Pierre Callet in Paris. When it was set up, with a capital of € 37,000, this family-owned company comprised 7 shareholders, including the 2 main shareholders, Rémy and Sylvie Brossel, who then shared 1,830 of the 1,850 total shares.

4.1.2. Presentation of the creators

Rémy Brossel, Medical Oncologist and Physicist, was medical director of a clinical research company until December 2009; he serves as scientific and medical director in Cell Constraint & Cancer SA.

After a degree in Physics and Chemistry, he became a MD, with a residency as a Hematologist-Oncologist in the hospitals of the Assistance Publique de Paris; he moved to California to develop a blood stem cell culture technique. Then he entered the pharmaceutical industry in 1983, at Schering AG, which he left in 1989 to create and take the direction of the Biologie & Industrie Limited (B & I). B & I is initially a biotechnology company developing monoclonal antibodies against breast cancer, and then becomes a clinical research service (CRO) company whose clients were laboratories in the pharmaceutical industry, biotechnology firms and institutional bodies.

A scientific council surrounds the direction. It consists of a mathematician, Daniel Gabay, a business leader in the field of medical equipment, Dr. Eric Peltier, former CEO of Novacyt, a researcher specialist in Electro-magnetism, Christian Chillet (PhD, CNRS / G2ELab), of a Pathologist, Dr. Jean-Marc Guinebretière (Institut Curie), a medical oncologist, Dr. Roy Weiner, (Tulane, US-LA) and Stéphane David, specialist in electromagnetism (PhD, CEA). This scientific council is convened regularly. Being informed of the progress made in the acquisition of the different stages of proof of concept and feasibility, his opinion is solicited by the management. The various skills gathered must make it possible to advise management on the validity of the scientific hypotheses and their industrial relevance.

4.2 KEY FIGURES (excluding co-development with industrial and before placing on the market)

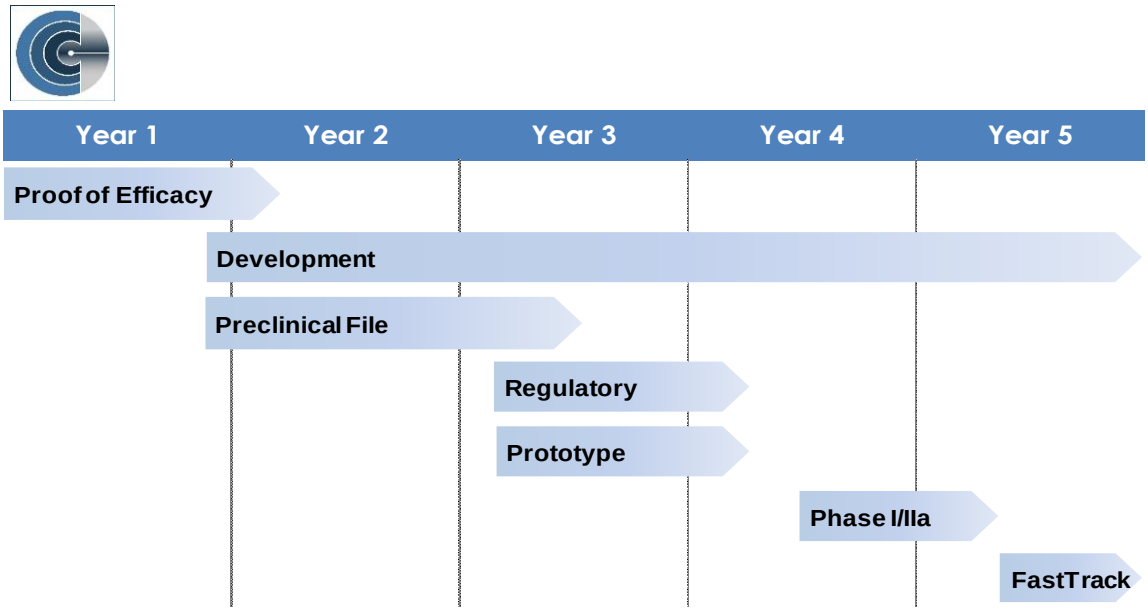
In euros	Executed 2017	Executed 2016	Executed 2015
Turnover	0	0	0
Operating profit	-89,018	-263,842	-42,335
Net profit after tax	-79,742	-274,701	-40,068
Number of employees	3	3	3

Year 1 means the year the funds are raised to demonstrate Proof of Efficacy.

Hiring:
- year 1: 1 researcher (young doctor)
- year 2: 1 project manager

Hiring forecast after Proof of Efficacy

	Year 1	Year 2	Year 3
			Cost (in K €)
1 PhD		160	16 0
1 Project Manager			150
Total		**160**	**310**



The schema assumes optimal resources.

4.2.1 The Product

Cell Constraint & Cancer SA develops a patented process (PCT WO 2015/004285) for treating cancer using purely physical and not biological means. In other words, it is not a drug, a molecule, a biological manipulation, genetic or immunological, a cell therapy.
We are based on the study of cancer with the mathematical and experimental tools of physics and not of biology. Our patent protects the possibility of applying a "Stress Field" (or field of constraint) (A set of pressures distributed in the tumor) to a tissue in vivo. This involves positioning magnetizable nanoparticles around the tumor and then applying a magnetic field gradient to the tumor / nanoparticle assembly from the outside. This results in a stress field applied to the tumor.

It has been known for more than 10 years that a stress field applied to an in vitro tumor slows its growth and, if we apply a sufficient stress field, leads to a return to normal non-malignant tissue (M Paszek 2005, F Montel 2011 and others).
The innovation concerns the transposability of in vitro 3D (three-dimensional cell culture) to in vivo, that is to say from test-tube to the animal.

The product is defined as the combination of two medical devices:

- **A magnetic field gradient generator** located outside of the patient. For patient, this generator will be quite similar in volume, cost, power, to a current MRI and therefore contains electromagnets in the animal prototype and superconducting magnets in the human prototype.

- **Magnetizable nanoparticles** located in the vessels around the tumor (neoangiogenesis). These particles act as a bioactuators and transform magnetic energy into mechanical energy.
These ferric nanoparticles are vectorized towards alpha v beta 3 integrins, overexpressed in tumor neovessels.

4.3 THE MARKET

This market is global right away. This is a highly regulated market. Class III Medical Device (MD) files are submitted to health authorities, in Europe country by country, in the USA to the FDA.
Buyers are, in France, public hospitals that have a radiotherapy and an oncology department and comprehensive cancer centers (private non-profit), starting with the most important centers.
For the Magnetic Field Gradient Generator (MFGG) which is a "heavy equipment". For the hospital departments, therefore subject to planning and ministerial authorization, it is necessary to provide for a negotiation for the installation of the first devices with specifications including a protected room, training, maintenance, upgradings, etc.).
The reimbursement by health bodies should be similar to what exists today for radiotherapy (key letter, such as Z, depending on the duration, the number of sessions...)
For consumables, NanoParticles (NP), the buyer is the hospital, the payer the health body with annual contracts. Reimbursement goes through a standard procedure.
The 10 million patients who die each year from cancer and are therefore therapeutic failures are ultimately potential users of the treatment.

Price estimation

The selling price of a Generator can be estimated at 2 M€.
The NP could get a good unit price: € 3,000.

The Market: The French example

The economic model is comparable to the installation of the last heavy equipment of oncology. Without going back to the replacements of Cobalts by linear accelerators (the last example of a physical cancer treatment device) or to CT scans, MRIs and PET scans are imaging devices that have quickly proved indispensable for treatment of cancer patients.
The implementation curve is similar for all those heavy equipments.
First a test phase, technical and clinical under ministerial control in reference centers; then an exponential growth to meet the needs of increasingly narrow population basins. Finally, a linear growth followed by a mature market platform.
In total, an S curve over 10 years.
Remember that this type of device first receives an authorization for a given organ. For example, the scanner was first used for brain imaging, then other indications lead to an acceleration of the market.

For the only indication: Pancreas cancer locally advanced, in the French market alone

	Year 1 (Centers of reference)	Year 2 (CHU and PBC large volume)	Year 3
Devices	3	5	8
Turnover	€ 6 million	€ 10 million	€ 16 million

Then, new indications

	Year 4	Year 5
Multiplicative factor (example: glioblastoma)	x2	x2
Devices	10	20
Turnover	€ 20 million	€ 40 million

Then years 5 to 10: 20 / year; 40 M € / year

Consumables: example on Pancreas Cancer

	Year 1	Year 2	Year 3	Year 4	Year 5
Cumulative CA	€ 1.125 million	€ 3 million	€ 6 million	€ 13 million	€ 27.5 million

On the basis of 375 patients per year treated for 15 days each with a single injection.
Then, linear growth of + € 14.5 million / year.
Again, a multiplicative factor, according to the indications and extensions of indication, is to be considered, not shown in this example.

This market is therefore potentially huge, but for the moment the Business Model is the search for an industrial partner capable and eager to accompany us in R & D with timelines, deliverables and milestones, and pre-determined capital contributions based on compliance with development specifications.
For that, it is necessary to engage a virtuous circle with publication of the results in scientific journals, participation in relevant meetings. The approaches of the industrialists are then very naturally on the basis of co-development preceding a license or a merge.

4.4 ACTIVITIES OF THE COMPANY

Cancer cell culture

- **In 3D** (3 dimensions) **in vitro**

The appearance of cell / tissue culture techniques in 3 dimensions allowed to study the influence of the pressures on the tissues in culture in a configuration much closer to the physiology than the old cultures in 2 Dimensions. Pressure can then be transmitted from outside of the culture cells / tissues grown from 100 to 2000 Pa pressure (Pascal) entrained by increasing the surface tension in the first publication, from M. Paszek in 2005. These pressures are those that allow in a 3D model of breast cancer in vitro to reverse the cancerization of a "breast acinus". An acinus is the small, spherical unit of secretion of milk by the mammary gland. Another publication (F. Montel, 2011) has confirmed these results on another model and using osmotic pressure.
Other authors (M. Bissell, M. Olcum, R. Jain...) used other models and other mechanical signals.

- **In 3D** (3 dimensions) **in vivo**

Proof of Concept

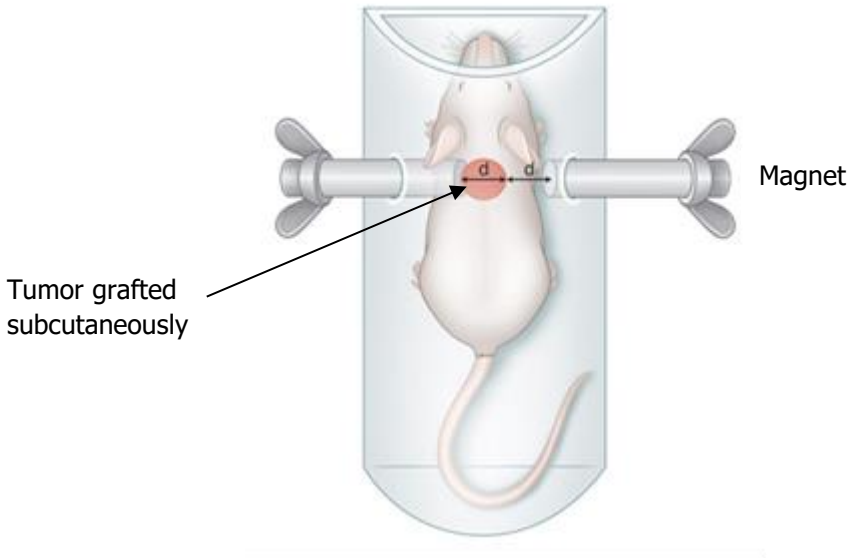
Feasibility

The company Altran who advised us in electrotechnics and carried out the first feasibility study worked with us at the beginning of 2011 and measured the gradients of the fixed magnets used. Their measurements confirm the estimates made in 2008 and give values in T / cm (Tesla per cm) compatible with a biological action.
Oncodesign also showed in late 2010, in a mouse study, with 100 nm ferric nanoparticles mixed with cells of the same type as those used in vitro (MDA-MB 321) that on the one hand the iron concentrations were sufficient, and the particles did not penetrate the tumor cells but remained around allowing for remote action, as required by the technology developed.
The tumor cells are injected into the mouse where they form a tumor. They are injected subcutaneously at the same time as the NanoP (NP). NPs are distributed around the tumor because of the large difference in free surface energy.

The tumor containing the particles is placed in a magnetic field gradient.

Our hypothesis is confirmed: the stress field, transmitted by the nanoparticles, is exerted on the tumor cells, and, according to the parameters (size / density / composition of the particles, amplitude, frequency of the magnetic field), modulates their phenotypic expression.

The experimental device used first in feasibility then in proof of concept in vivo is represented in the figure below:



Proof of Concept: the concept was validated in 2016.
There is a significant difference between the treated group and the control groups. This difference concerns the volume of the tumor measured in vivo which is very significantly decreased (p = 0.015) in the treated group compared to the 3 control groups (with particles and without gradient, with gradient and without particles, without gradient or particles). There is also a significant difference in favor of the treated group when measuring the surface of the living tumor, ex vivo, on digitized histological sections (p <0.05).

Results

Groups of grafted mice	**Median Tumor Volume (in mm^3)**	**p (significance of the difference)**
Treated groups	529	p = 0.015
Control groups*	1,334	
Average (in mm^2)	**Tumor area on histological sections digitized ex vivo**	
Treated groups	7.7	p = 0.001
Control groups	23.1; 21.4; 26.8	

* Three groups of mice: with particles only; with gradient alone; without particles or gradient

In vivo: Proof of Efficacy

The principles

The possibility of therapeutic use, of course, opens up enormous opportunities.
The method fits into the current conception of carcinogenesis: impossibility of thinking the cancerous transformation without integrating the interaction Extra Cellular Matrix (ECM or stroma) / cancerous tissue; orientation of cancer therapy towards a modulation of the phenotype rather than the search for "the death of the last cell".

MEC (or stroma) has long been considered a "support tissue" without a specific role. It has become a mandatory part of decision-making by cells / stem cells / tissues to change their phenotype. In other words, the MEC / Tissue pair is inseparable in the mechanisms of phenotypic modifications, such as cancerization, and even more so in the maintenance of the normal tissue organization of the tissues from which most cancers (the epithelia) are born.

Today, the ECM is first of all one of the two tissues that compose the cancer organ and is located around the tumor tissue itself.

The arrival of Physical Oncology in the scientific reasoning of biology consists in integrating mechanics into the signals sent by the (micro) environment (ECM) to cells and vice versa, in parallel with biochemical signals; It has also been necessary to integrate the fact that the genetic and epigenetic mutations (not related to DNA) of cancer cells are partially under the domination of this microenvironment.

Mina Bissell, 2009: "In oncology, the tissue phenotype is dominant over the cell genotype".

Some of the mechanisms of action are known: transmission of forces to the nucleus via the cytoskeleton, and maintenance of the Euclidean architecture of normal cells, while the cancerous architecture is fractal.

Experimentation

Animal testing will be preceded by two feasibility studies.

Biological feasibility comparing iron intake by **vectorized NanoParticles** and by **vectorized Liposomes** and iron-loaded

The comparison will be done on:

- Injection of the particles and liposomes in a batch of 2 times 12 mice transplanted at 8 days of interval, then assay of the iron in the tumors taken later, at 1 hour, 3 days, 1 week, 2 weeks.

Choice of vector and possible adaptation of the injection protocol if there is a significant decrease in the amount of iron at 8 days.

Physical feasibility

On a batch of 6 grafted mice, injection of the vector chosen under real conditions of treatment in the gradient generator with anesthesia of one hour. Monitoring of body temperature, mortality, autopsies.

Randomized experimentation

In vivo amplification of human pancreatic cancer grafts from "PDX" (surgical waste, obtained after patient consent); 10 weeks.

Orthotopic graft

Random constitution of 4 groups of mice.

The treated group: 24 mice injected and subjected to a gradient;

The control groups:

- 12 mice in spontaneous evolution without injection or gradient;
- 12 mice with gradient-free injection;
- 12 mice without injection with gradient.

Figures are given subject to approval of the statistical analysis plan.

Treatment: gradient exposure, under anesthesia, for 1 hour per day, for 5 days per week, for 2 weeks, in 36 mice; At the rate of 6 mice per day: 36 weeks.

Monitoring:
In vivo tumor volume by ultrasound 3 times a week.
X-rays 1 time per week
Samples at one week, by sacrifice, 1 batch of 6 animals in the treated group and four from the gradient-only group, measure of the histological tumor volume, quantification of iron around the tumor.
Daily monitoring of well-being, behavior and possible mortality. If mortality or sacrifice is needed for discomfort, specimens for histology and iron determination, and replacement of the mouse in its group.

After 15 days of treatment, sacrifice, macroscopic autopsy.

Collection of tumors and sharing in two parts: one half frozen (snap-frozen) and the other half in formalin for shipment to the pathology laboratory.

Histology:
Usual markers of apoptosis, growth, cell death and differentiation estimation.

Quantitative histology:
Measurement of tumor fractal coefficient on digitized sections.

Reports:
Quality assurance.
Experimental.
Statistics.
Articles: after feasibility; after results of the randomized experiment.

4.5 OBJECTIVES AND AIMS OF THE PROJECT

The objective of the European project is to develop a method to be active in an animal model: the "orthotopic" transplant (eg "pancreas in the pancreas"), currently the most relevant model for a possible extrapolation to humans.

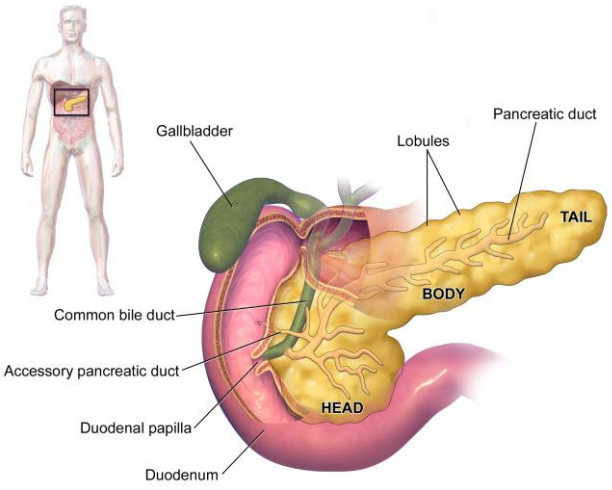
Moving from Proof of Concept to Proof of Efficiency is a change of scale and requires two new devices: a gradient generator and vectorized NPs. But it is essential to emphasize that by using a physical (and not biological) method of action on the tissues, one virtually eliminates the hazard of the biological. This biological hazard which is that of the pharmaceutical industry and which relates to the efficiency but especially to the toxicity is here reduced to little things even if, after the animal phase, in application to the Human, there can be surprises.
This hazard is what sends 9 candidates - drug out of 10 in the trash.
We can therefore say that this project is not "early" in the sense of the pharmaceutical industry whose approach, vocabulary and methodology permeate all therapeutic research.
From this proof of efficacy in vivo, the probability of a conserved efficacy in humans is much greater than in the development of a "molecule".

The principle remains the same: our patent protects the ability to apply "a stress field" (which can be approximated in a first approach, as a set of forces and pressures, or by expanding the concept, as a tensor field) to a tissue in vivo. This involves positioning magnetizable nanoparticles around the tumors and then applying a magnetic field gradient to the tumor / nanoparticle assembly from the outside. Nanoparticles then behave like "BioActuators" transforming magnetic energy into mechanical energy. This results in a stress, a pressure applied to the tumor.

The first indication: pancreatic cancer.

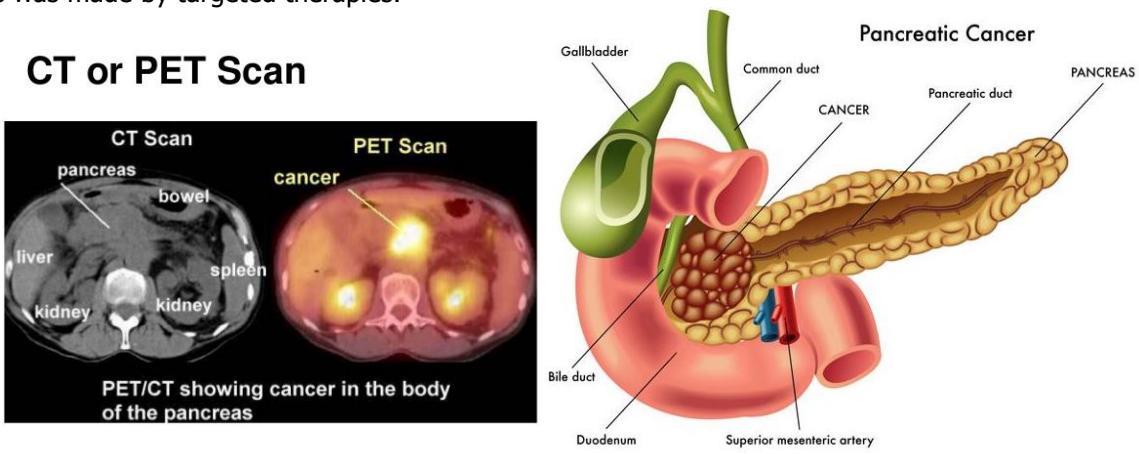
4.6 MEDICAL JUSTIFICATION

The pancreas is an organ located very deep in the abdomen.



Pancreatic cancer is a malignant tumor whose prognosis overall remains very poor. The chances of survival at 5 years range from 5% for non-operable cancers, to 30% when the tumor could be operated during the discovery.

In France, there were 12,000 new cases in 2016 and 11,000 deaths, and these numbers are increasing year by year.
The diagnosis of pancreatic cancer is most often made at an advanced stage of the disease, which explains why survival at 5 years is so poor. The number of new cases is increasing from year to year and, for the first time, there were more deaths in 2016 from pancreatic cancer than from breast cancer.
No progress was made by targeted therapies.



CT scan (left) and PET scan (right) showing pancreatic cancer

There is no known cause for pancreatic cancer, nor for its growth anywhere in the world.

Surgery is the standard treatment, the only one that heals, if the patient's condition allows it. The intervention is difficult and heavy.

But as we have seen, operable patients from the outset are only a minority: 10% and a majority of them will relapse.

Chemotherapy, until recently, was exclusively palliative. The recent introduction of the 'Folfirinox' protocol (often called Abraxane Gemcitabine in the US), a combination of 3 chemotherapies, made it possible to turn non-operable tumors into operable ones and to significantly prolong palliative survival. But this protocol, very heavy, is only applicable to a minority of patients.

Immunotherapy is a real and exciting innovation. It is in its infancy and, in pancreas, we still do not discern its possible applications, except in a very small minority of patients said with 'microsatellite instability'.

The treatment of pancreatic cancer is, whatever the technique used, a cumbersome, complex and uncertain process.

Faced with existing treatments, Cell Constraint & Cancer offers a new approach to the treatment of pancreatic cancer using mechanical signals and not biological signals (i.e. molecule, drug, immunology).

Worldwide, there are 400,000 new cases of pancreatic cancer every year.

4.7 COMPETITION

There is currently no direct competition using mechanical signals in vivo for therapeutic use.
Targeted therapies and especially immunotherapy, are to be considered synergistic. Indeed, immunotherapy is the first effective anti-cancer treatment that takes into account the interaction between the tumor and the matrix and recent articles (A. Miyazawa et al., 2018, J Hong et al., 20016) show that the rigidity of the matrix increases the possibility of immunotherapy.

4.8 CONTEXT AND SCIENTIFIC AND TECHNICAL ISSUES

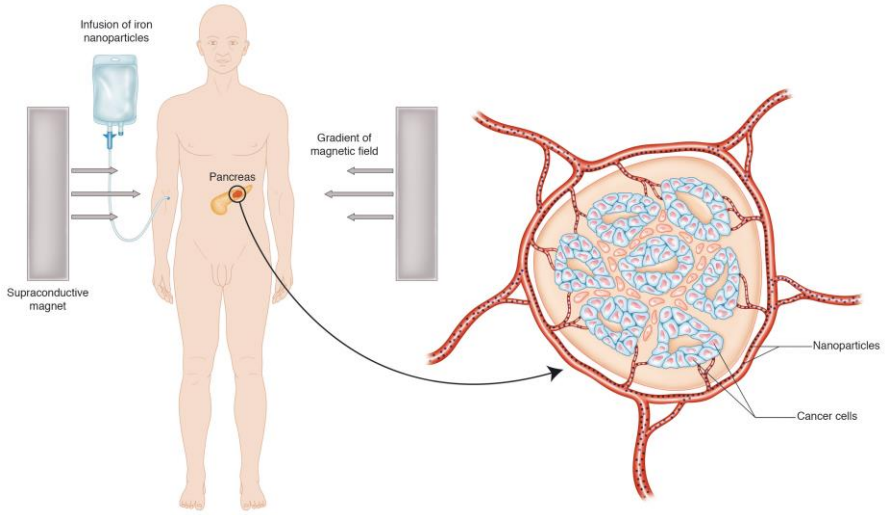
Instrumentation and injectable state of the art

The design and construction of Magnetic Field Gradient Generators (MFGGs) are in the field of electrotechnics, a long-standing engineering science.

For the Proof of Concept published on April 21, 2016, permanent magnets were used as MFGG.

For the Proof of Efficacy, the animal demonstrator consisting of electromagnets dedicated for this use has been designed by the G2E Lab (CNRS Grenoble). But MFGGs are already manufactured by the medical imaging industry for a new technique (Magnetic Particles Imaging) and could be used for our purposes.

For use in the patient, it will be necessary to use superconducting magnets. The prototype of MFGG for human use will have a volume, a cost of manufacture and a price (2 M€) similar to those of a current MRI, which explains why we are looking for an industrial partnership with a manufacturer of this type of device.



The design and manufacture of vectorized ferric nanoparticles are well mastered. Many public and private laboratories have this know-how.

The adoption of these two technologies for in vivo therapeutic use is in the domain of manufacturers with R & D departments able to follow the standards used in health products.

4.9 DEVELOPMENT STRATEGY

We believe that the decisive step is the In Vivo Proof of Efficacy, which marks the end of research, followed by the publication of an article in a major scientific journal and conference presentations.
For this last stage of research to resort to the shareholders is insufficient. CC & C presents two public grant application files:

- To the European Commission with the submission of a file 'FET Open' under the H2020 program. We are asking for 1.9 M€ as part of a consortium to conduct the animal experiment; this consortium brings together 3 countries and the Inserm unit of Bichat-Paris 'Inflammation and Cancer Research Center' is the leader of this project, mounted on our initiative.

- In the USA with a request to the National Cancer Institute with the help of Prof. G. Pratx (Stanford University) to resume in vitro the modeling of the field of constraint with the means of a Californian university.

Then comes the development that we estimate at 2 years before clinical experimentation in the patient.

In parallel we continue our preliminary contacts with an industrialist of magnetic field gradients (MRI) and who is interested in the development of a device for therapeutic use. This industrialist could become a partner for further industrial development: manufacturing, certification, marketing and sale of heavy equipment to hospitals.

The development in its regulatory part will be subcontracted to a 'CRO' of which we will be the manager. The stages are precisely defined by European laws and regulations, for toxicity, pharmacology... These animal experiments are the pre-requisite before clinical research (Phase I / IIa in the cancer patient). To finance this development, it will be necessary to set up a first "Series B" round of financing with institutional and private investors.

Upon completion of the research, CC & C will seek industrial partners to co-build the prototype for human use, to make nanoparticles (or liposomes).

4.10 THE RETURN ON INVESTMENT AND THE MARKET

4.10.1. Return on investment

Everything contributes to a possible short development time, over 4 to 5 years, so much less than a therapeutic molecule. Similarly, investments would be relatively modest due to the use of already known components, generator and particles. Ideally, the industrial partners are medical imaging equipment manufacturers, or contrast media manufacturers, especially MRI nanoparticles manufacturers.

The first stages of development are inexpensive.

Intellectual Property requires investment over years, coordinating the electrical engineering and biology teams.

The return on investment is short for a therapeutic method, which is explained by the use of the laws of physics allowing modeling and development in parallel.

At present, no framework contract has been concluded with any of our suppliers.

4.10.2. Potential market

Pancreatic cancer is our first indication. The first indication will be locally advanced cancers of the pancreas, ie 30% of these cancers. The goal is to make them operable, surgery is still the only way to cure pancreatic cancer.

1) Some numbers

In the USA in 2018 (forecast)

It is a growing cancer: today the fourth leading cause of cancer death.
In 2016, there were more deaths in Europe from pancreatic cancer than from breast cancer.

Two indications are possible:

- the first for 'Locally Advanced' (locally evolved), that is inoperable immediately but without metastasis, in order to make them operable.
- the second for metastatic patients from the outset with the aim of palliating signs and symptoms.

Obtaining an indication requires a clinical study. The first clinical study planned is in Locally Advanced. This study, like the following ones, is of short duration (<1 year) and on few patients, thus inexpensive.

The locally advanced pancreatic cancer represents about 30% of patients, or about 12,000 patients / year in USA. The following indications will be cancers whose current treatment is very insufficient (primary cancer of the brain, liver...). But, in the long run, the 10 million deaths per year are failures of treatment, and ultimately potential beneficiaries of this new approach to cancer.

2) Treatment

In a purely intuitive way we can imagine a radiotherapeutic treatment in its timing: 5 sessions per week for 4 to 5 weeks with an injection of nanoparticles per week.

A machine of this type could have a price of the order of MRI (2 M€).
Consumable could have a large margin, as is often the case when there is a coupling with a machine and be of the order of 3,000 € per injection.

3) Market strategy

We address first cancers with few treatment resources such as the pancreas and without development of new treatment (such as targeted therapies or immunotherapy) significantly changing overall survival.

The future: few current therapeutic solutions, no major predictable innovation, locally evolved / metastatic cancer; this can be declined in numerous locations: primary liver cancer, primary bile ducts, glioblastoma (brain), rectum, esophagus, ENT, etc. In total, perhaps a quarter of the one million new patients in the US could be affected.

Some of these tumors are rare in the so-called Western countries but, on the other hand, very common in Asia, such as stomach cancer or primary cancer of the liver.

The installation of this type of machine, country by country is a bit long (authorization, environment, staff training, etc.) but the growth is rapid, as shown by the installation of MRI and then closer to us, PET Scan.
We therefore have a S-curve growth model with first an exponential growth spanning 5 to 6 years, followed by a linear increase over 10 years.

4.11 RISK FACTORS

4.11.1 Industrial and environmental risk

The type of material envisaged presents electromagnetic risks which will have to be approved, within the framework of the CE marking, by a notified body, like the G Med-LNE in France or getting a PMA from the FDA in the US. The applicable regulations are fairly stable. Injectable ferric nanoparticles are not very toxic because they are recycled by the body and do not raise the same controversies as those which are disseminable in the environment or accumulable in the body.

4.11.2 Risk on intellectual property

This type of innovation must be supported by a permanent flow of protections, taking into account the US specificities, both for the production of equipment and consumables. Risks related to non-patentable or not yet patented data, processes and know-how are a permanent concern, theoretically covered by confidentiality agreements, but we know that neither the academic world nor the French are overly sensitive to this aspect of things.

4.11.3 Financial risk

CC & C is a "Start -up" in Med Tech. It therefore has all the characteristics of this type of society, including a high risk of early mortality.
The risk of insufficient liquidity is common in this type of innovative company that generates revenue after several years of R & D. Capital will be prioritized by capital increase or current account provision. Any cash invested would be in cash or equivalent.
There is no signed insurance policy to date, but the company is committed to signing a contract as soon as possible on the responsibility of directors, professional insurance for travel, liability and loss of business in case of the disappearance of the leaders.

4.11.4 Risk during development, Ineffectiveness / Toxicity

It must also be emphasized that this is not about the development of a molecule. Both components of the system are based on known and quantifiable techniques. The application of a physical method guarantees much less randomness than the development of a therapeutic molecule. It can be predicted - with the usual precautions - that unlike molecules that are 80% to be removed during development for toxicity reasons, what we know about the use of field gradients and nanoparticles of this type in humans predicts good tolerance.

4.11.5 Risks related to the non-realization of the present capital increase

In order to provide financing for its Research activity for the next three years, the company decided to increase its capital by issuing 79,015 BSA (warrants) to be exercised at a unit price of € 20 until December 31, 2018.
The technique of issuing stock warrants instead of a direct issue of shares provides more flexibility to the company in organizing the raising of capital and avoids the risk for the company and for subscribers of non-realization of the capital increase. Indeed, a direct issue of shares requires the recognition of at least three quarters of the capital increase that has been decided while no minimum is necessary to record the exercise of share subscription warrants.

4.11.6 Risks related to the organization of the company

The most sensitive points are management, outsourcing and investor research.

The Company's activity is highly dependent on the quality and level of expertise of its future scientific staff as well as its management staff. The Company's dependence on its scientific and management team is a key issue in the analysis of its growth prospects. The Company's continued growth depends on its ability to attract, motivate and retain highly qualified personnel. Thus, in the coming years, the Company will have to implement a recruitment of highly qualified personnel, capable of carrying out research and development or commercial activities with high added value.

Currently, academic partners provide support for our expertise. To carry out its development programs, the Company will manage its projects through a light internal research and development team and will rely heavily on outsourcing to specialized companies for the conduct of studies.

4.11.7. Exceptional facts and litigation

To the best of our knowledge, there is currently no litigation, exceptional events or legal risk that could affect CC & C's financial position, results, business or assets.

Chapter 5

BALANCE SHEET AND INCOME STATEMENT

Documents available on the site: https://secure-cellconstraintcancer.com/downloads/bilan-et-compte-de-resultat-2017.pdf

Chapter 6

INFORMATION ABOUT THE ADMINISTRATION AND THE MANAGEMENT OF CC & C SA

6.1 BOARD OF DIRECTORS

The Company takes the form of a Limited Company with a Board of Directors whose operation is set out in the articles of association (available on request).
In accordance with the statutory provisions, the Board of Directors is composed of at least three (3) members and at most eighteen (18) members.

The council is composed to date of:

Name	Mandate and function	beginning mandate	End mandate	Number of shares held
Barthélémy BROSSEL	President	April 3, 2014	AGO ruling on the accounts at 31/12/20 20	157
Albert ROUDAUT	Administrator	June 3, 2016	AGO reports on the accounts as at 31/12/2022	2,765
Vincent BROSSEL	Administrator	April 3, 2014	AGO reports on the accounts at 31/12/2020	7

The Board may expand to other persons who have subscribed to the shares issued on the occasion of this capital increase.

6.2 CONVICTION OF THE MEMBERS OF THE BOARD OF DIRECTORS

To the best of the Company's knowledge, in the last five years:
- no Director has been prevented by a court from acting as a member of an administrative, management or supervisory body of an issuer or from acting in the management or conduct of the business of a issuer;
- no Director has been the subject of incriminations or official public sanctions pronounced by statutory or regulatory authorities.

6.3 OTHER RESPONSIBILITIES BY ADMINISTRATORS AND DIRECTORS FROM FIVE (5) YEARS

Name	Address	Mandate and function	Other offices held	Offices held in the last 5 years
Barthélémy BROSSEL	10, bd Louis Salvator F13 006 Marseille	President	no	CC & C Director
Albert ROUDAUT	26, rue de la rivière 72190 Saint-Pavace	Administrator	no	no
Vincent BROSSEL	51, rue Mouzaia - 75019 Paris	Administrator	no	no

6.4 CONFLICTS OF INTEREST

None

6.5 REMUNERATION AND BENEFITS

6.5.1 Compensation and benefits in kind of officers

Barthélémy Brossel is a part-time employee as communication manager.

6.5.2 Total amounts set aside or accrued by the Company for the Purpose of Paying Pensions, Retirement or Other Benefits to Officers

No provision has been made for this purpose.

6.6 FUNCTIONING OF THE BOARD OF DIRECTORS

6.6.1 Directors and mandates

The directors referred to in paragraph 6.1. above have been designated in the bylaws and will therefore have their term expire at the end of the Ordinary General Meeting of Shareholders called to approve the financial statements for the fiscal year ended December 31, 2020.

6.7 CONTRACTS BETWEEN THE ADMINISTRATORS AND THE COMPANY

See § 6.5.1

6.8 AUDIT AND REMUNERATION COMMITTEE OF CC & C

It is not envisaged in the short term to set up an audit and / or remuneration committee within the Company, given its size and the distribution of powers envisaged to carry out its activity.

6.9 CORPORATE GOVERNANCE

The Company does not follow the corporate governance recommendations of companies whose securities are admitted to trading on a regulated market.
Given its size, the Company does not consider the implementation of such recommendations as essential nor relevant at this stage.

6.10 SHARE ALLOCATION PLAN

None

6.11 INFORMATION ON TRANSACTIONS WITH THE ADMINISTRATIVE AND MANAGEMENT BODIES

None

6.11.1 Conventions in force on the current financial year

None

6.11.2 Loans and guarantees granted or granted to the administrative and management bodies

None

6.12 EMPLOYEE BENEFITS

It is not currently programmed any form of employee incentive through the establishment of a Business Savings Plan or any other technique.
The setting up of such a means of motivation and loyalty of employees may be proposed later at a General Meeting of Shareholders.

6.13 EXTERNAL AUDITOR

See § 1.3

Chapter 7

RECENT DEVELOPMENTS AND FUTURE PROSPECTS FOR CC & C SA

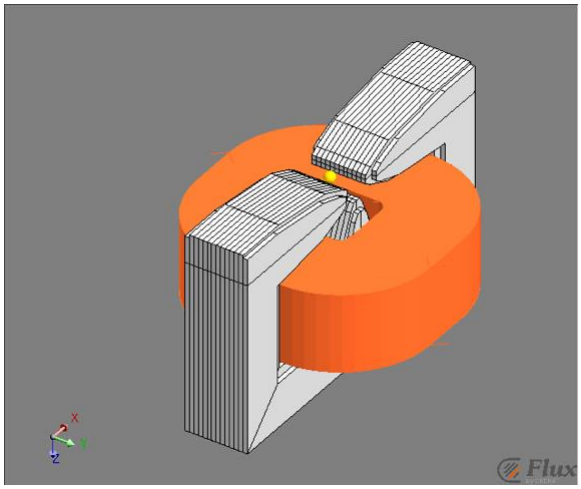
7.1 RECENT EVOLUTION

An article presenting the validation of the Proof of Concept was published on April 21, 2016 by the journal PloS One by R Brossel et al. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0152885
A presentation was made on June 26, 2016 in Boston at the AACR conference and published in Cancer Research.
http://cancerres.aacrjournals.org/content/77/2_Supplement/A41

Moreover, the PC T / WO2015 / 004285 patent filed on July 12, 2013 is in the process of "national phase procedure" in Europe, the United States and Japan. http://www.google.dj/patents/WO2015004285A1?cl=en

A multi-year collaboration with G2Elab leads to a gradient generator prototype

The G2Elab is a reference in Europe on electromagnetism. This was the laboratory of Louis Noël (Nobel 1970), it is today one of the most innovative laboratories of the CNRS in this discipline. The generator designed at G2Elab is original in its design.



Tumor 1 cm in diameter, yellow
Electromagnet in orange with three poles surrounding the tumor

It allows to deliver a large gradient (50 T / cm) in the middle of an animal 3 cm in diameter, in a tumor 1 cm in diameter. Circulation cooling is provided.
This generator has been designed to be compatible with the environment of an animal testing laboratory.

Two other partnerships
A European funding project will be asked in May 2018 with three partners: One academic in France for animal experimentation as well as two other academic laboratories: one in Belgium for nanoparticles, the other in Greece to study liposomes loaded with iron.
An experimentation is planned with Stanford University (California), funded by the National Cancer Institute.

The patent

A valuation of the patent filing was made at 353,192 euros. This patent is the main asset of CC & C.
A valuation of the company has been made, which you will find on the infographic of this prospectus.

Return on investment
The planned output goes through a period of cooperation with an industrialist mastering the technique of superconducting magnets required in the patient.
This period, usually less than 2 years, will include the usual Milestone, Deliverables, Go / No Go and must lead to a purchase of CC & C by this manufacturer, at a time scale of 4 to 5 years.

By analogy, one should remember the recent fate of Biotech companies in immunotherapy: concept in the 90's, patent filing at the beginning of the 21st century and repurchase in 2010 for amounts between $ 400 and $ 2 B.
Admittedly, analogy is not a comparison (long development time since biological product, biological hazard) but the orders of magnitude will be the same.

7.2 DEVELOPMENT PERSPECTIVES OF PHYSICAL ONCOLOGY

The concept, still little known, but progressing in scientific circles, of the possibility of influencing the phenotype of cells / tissues by purely physical means opens enormous prospects. This "Physical Oncology" has spillover effects in many scientific fields: tissue engineering, morphogenesis, embryology, organ reconstruction... It also has implications for our understanding of the evolution and role of DNA in biology.

For now, "Physical Oncology" gives rise to products (microfluidics, circulating tumor cells…), but not to therapeutic project competing with ours.

In the USA, the NCI has promoted since 2009 the establishment of a group "physical sciences - oncology groups" that combines the best teams of bioengineering and oncology with the objective of measuring the physical parameters of all models in vitro oncology. In Singapore, the Institute of Mechanobiology works on themes similar to ours, but in vitro.
Surprisingly among the many projects of these institutions there is no therapeutic program based on in vivo physical input and physical output.

7.3 THE MEANS OF DEVELOPMENT

CC & C must fund the end of the research, the Proof of Efficacy.

In order to perform the experimentation, we apply to a European call: FET Open RIA with a consortium.

The development is estimated at 5 M€ (3 M€ for the pre-clinic and 2 M€ for the clinic) and will go through an agreement with an industrialist familiar with MRI or MPI imaging.
Several financing instruments are envisaged to ensure the sustainability of the company:

1) - continuation of capital increases,
2) - participation in a research consortium in association with public research organizations as soon as our cash flow permits,
3) - access to the Free Market, also conditioned by our cash,
4) - appeal to investors and Business Angels for this seed period, traditionally the most difficult to finance.

7.4 INDUSTRIAL DEVELOPMENT PROSPECTS

Industrial development involves collaboration followed by incorporation into one of the companies that master the superconducting magnets for medical use, a dozen firms worldwide.
The contact with the Direction or the department of technological watch of these companies will be done at the end of the Proof of Efficiency, thus once established the clinical credibility of the method.

7.5 BIBLIOGRAPHY

A good introduction in English to "Forces and Cancer"
Erika Jonietz "The forces of Cancer"
Nature, November 22, 2012, 491, S56-S57
http://www.nature.com/naturejobs/science/articles/10.1038/491S56a

The reference article
Matthew J Paszek, Nastaran Zahir, Kandice R Johnson et al.
Tensional homeostasis and the malignant phenotype
Cancer Cell 2005, 8; 241-254
http://www.sciencedirect.com/science/article/pii/S1535610805002680

A publication of the Institut Curie / ESPCI
Fabien Montel, Delarue Morgan, Jens Elgeti et al
Isotropic stress reduction cell proliferation in tumor spheroids
New J. Phys. 2012, 14; 1-14
http://iopscience.iop.org/1367-2630/14/5/055008

Interaction between mechanical signals and genetics
Ning Wang, Jessica D Tytell and Donald Ingber
Mechanotransduction at a distance: Mechanically coupling the extracellular matrix with the nucleus
Nature Reviews, 2009, 1075-81
http://www.nature.com/nrm/journal/v10/n1/abs/nrm2594.html

Interaction between mechanical signals and immunotherapy
Miyazawa, A., Ito, S., Asano, S., Tanaka, I., Sato, M., Kondo, M., & Hasegawa, Y. (2018). Regulation of PD-L1 expression by matrix stiffness in lung cancer cells. *Biochemical and Biophysical Research Communications*, *495* (3), 2344-2349.
https://www.ncbi.nlm.nih.gov/pubmed/29274784

Jiang, H., Hegde, S., Knolhoff, BL, Zhu, Y., Herndon, JM, Meyer, MA... & Pachter, JA (2016). Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nature medicine, 22 (8), 851.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4935930/

Thorsten M Koch, Stefan Münster, Navid Bonakdar et al.
3D traction forces in cancer cell invasion
PLoS One, 7 (3), 1-9
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0033476

A publication on "Ex vivo"
Marija Plodinec, Mark Loparic, Christophe A Monier et al.
The nanomechanical signature of breast cancer
Nature Nanotechnology, 2012, 7; 757-765
http://www.nature.com/nnano/journal/v7/n11/abs/nnano.2012.167.html

By the team of Valerie Weaver who succeeded Mina Bissell (California)
Darci Butcher, Tamara Alliston and Valerie M Weaver
A tense situation: Forcing tumor progression
Nat. Rev. Cancer, 2009, 9 (2); 108-1225
http://www.nature.com/nrc/journal/v9/n2/abs/nrc2544.html