CC&C

CELL CONSTRAINT & CANCER

EXECUTIVE SUMMARY

PITCH

Cell Constraint & Cancer SA, France 13280

A disruptive innovation in oncology: how to use mechanical (non biological) signals to treat cancer?

First application: the pancreatic cancer.

• Proof of Concept in 2016: '**Action of Mechanical Cues in vivo on the Growth of Tumor Grafted subcutaneously'** (Published 21 April 2016, PloS One, R. Brossel et al). Http://dx.doi.org/10.1371/journal. pone .0152885

This 'Proof of Concept' in vivo was performed in collaboration with the 'Institut Curie', Paris.

We analyzed the results with Dr. JM Guinebretière (pathologist, Institut Curie): the concept is validated. Indeed, there is a very significant difference in tumor growth between the tumors treated with 'stress field' (or constraint field) and control groups in vivo by measuring tumor volume, and ex vivo, on digitized biopsies.

Next step: Proof of Efficacy: Action of mechanical signals on an 'orthotopic' graft of human pancreatic cancer in a mouse pancreas.

The product, a combination of two medical devices: a magnetic field gradient generator and magnetizable iron nanoparticles. The nanoparticles are located around (not in) the tumor and act as 'BioActuators', transforming magnetic energy into mechanical energy. The therapeutic agent is thus a 'stress field' (an ensemble of forces and pressures).

To sum up, Cell Constraint & Cancer (CC & C) is a Medtech engaged in a new approach to cancer research. Our disruptive innovation (patent PCT WO 2015 004 285) involves the application of mechanical signals (constraint / stress field) in the treatment of cancer.

Physical Oncology is defined as the study and treatment of cancerous tissue using the laws of mechanics and not biology.

This new approach to cancer radically changes our views on tumor development and therapeutic solutions.

CC & C is protected and has an innovative approach.

Today we propose an experimental follow up: get to show action on human pancreas cancer tissue grafted in mouse pancreas. Obtaining this' Proof of Efficacy' in vivo open perspectives in the treatment of tumors for which current therapies are insufficient, as locally advanced pancreatic cancer, unresectable. This would be the first therapeutic application of 'Physical Oncology'.

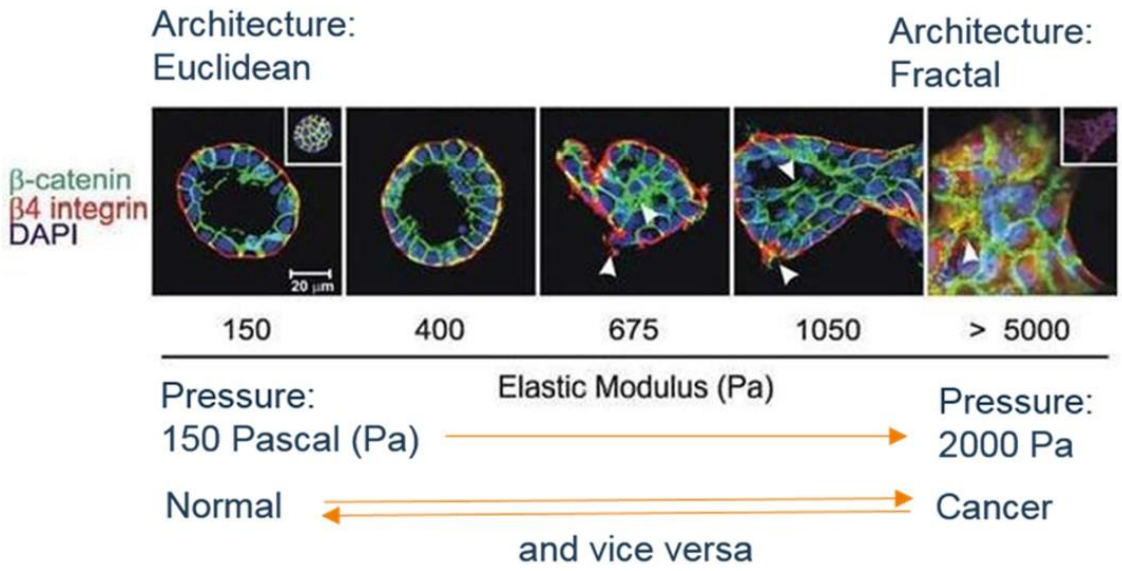
Demonstration of Proof of Efficacy of our process allows for consider a switch to man in 2024. We have already started a biological and physical feasibility study of the Proof of Efficacy planned in 2018/9.

SCIENTIFIC ISSUES

'Physical Oncology' is poorly represented in Europe, but very active in the United States where it was born (see Office for Physical Sciences and Oncology, NCI, http://www.physics.cancer.gov/ and Asia (Institute of Mechanobiology, Singapore) http://www.mbi.nus.edu.sg.

The first article: Paszek MJ, *et al*. (last author Valerie Weaver) (2005) Tensional homeostasis and the malignant phenotype. *Cancer Cell* 8(3):241-254

Figure 1



(With permission of M.Paszek)

The only modified parameter is the pressure around an acinus (elementary unit of milk secretion) of the human mammary gland cultured in 3 dimensions. This increase in surface tension, from 150 to > 5000 Pascal, is accompanied by architectural and biological changes.

From left to right, the initially Euclidean (normal) architecture becomes fractal (cancerous).
From left to right, we see activated proteins that accompany the cancerous transformation. This phenomenon is reversible.

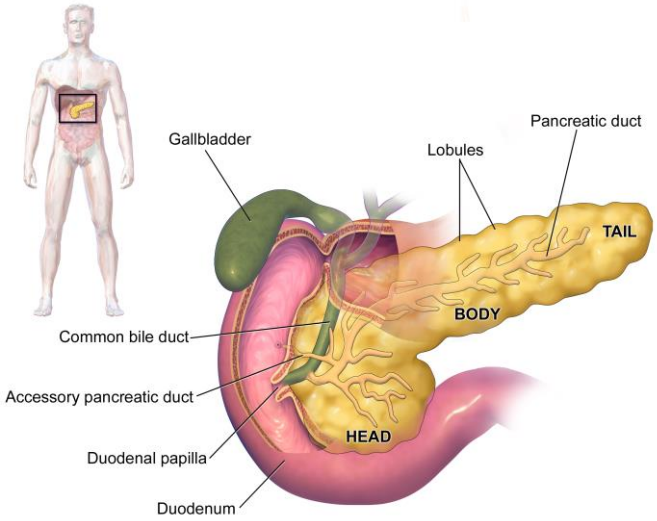
Our patent PCT / WO 2015/004285 protects the ability to apply stress to tissue in vivo. To do this, we position magnetizable nanoparticles around tumors and then apply a magnetic field gradient to the tumor via a magnet, from the outside. Nanoparticles are vectorized on alpha v beta 3 integrins overexpressed in tumor neovessels. This results in a constraint applied to the tumor: in fact, the nanoparticles act as "BioActuators" transforming magnetic energy that comes from the outer magnets into mechanical energy directed towards the tumor. The possibility of acting on a tumor using stress has been widely demonstrated in vitro in 3-dimensional tumor culture (M Paszek 2005, F Montel 2011 and others).

Our innovation relates to the portability of in vitro 3D (tissue culture in 3 Dimensions) to the in vivo. In other words, M Paszek et al (2005), F Montel et al (2011) and others have shown the ability to act on a cancer tumor, by physical signals, but only in vitro; CC & C applies the same principles (application of a constraint / stress field in cancer tissue), but in vivo in animal.

MEDICAL NEEDS

The pancreas is an organ located deep in the abdomen.

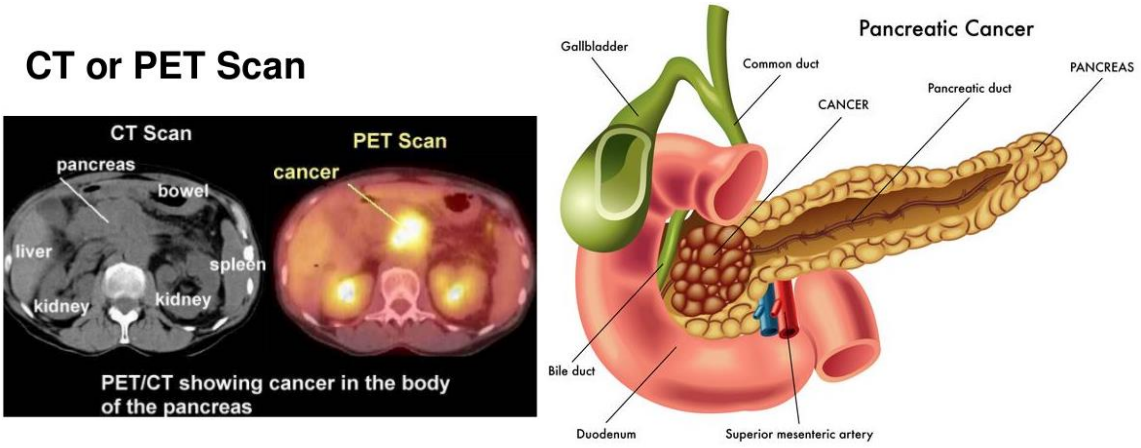
Figure 2: the pancreas in the human body



Pancreatic cancer is a malignant tumor whose prognosis is generally poor. The chances of survival at 5 years range from 5% for inoperable cancers, to 30% when the tumor could be operated when discovering.

In France, there were 12,000 new cases in 2016 and 11,000 deaths, and these numbers are increasing year by year. In the US in 2018: 52 300 new cases and 42 800 deaths.
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 in Europe from pancreatic cancer than from breast cancer.
There is no progress made by targeted therapies.

Figure 3: pancreatic cancer



A CT Scan (left) and a PET Scan (right) showing a 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 cure, if the patient's condition allows. This is a heavy and difficult operation.
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 (in the US often called Abraxane Gemcitabine), a combination of 3 chemotherapies, made it possible to make operable tumors non-operable from the outset 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 can not yet discern its possible applications, except in a very small minority of patients called '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 (molecule, drug, cells, immunology, ⋯).

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

FINANCIAL REQUIREMENTS

The financial needs of CC & C can be summarized as follows:

- End of Research: Proof of Efficacy
- Duration: 1 year
- Needs: 250 K€

- Pre-Clinical Development and Intellectual Property
- Duration: 2 years after the Proof of Efficacy
- Needs: 4.3 M €

- Clinical development: Phase I / IIa
- Needs: 700 K€

For the current year, we hope to collect around € 250,000 to carry out the Proof of Efficacy. European funds are requested: CC&C apply to a FET Open program (H2020) with three European academics.

INDUSTRIAL PARTNERS

For holding this Proof of Efficacy, we can rely on the recent emergence of imaging machine interestingly (Magnetic particle Imaging) using large gradients (2-5 Tesla / m) generated by electromagnets. Or, more probably, the European funds could be used to build an animal demonstrator made of strong electromagnets (up to 50T / m).

The aim is to engage after the Proof of Efficacy a collaboration with an industrial firm mastering the technique of superconducting magnets, that are necessary for Human beings, and the sale of heavy equipment to hospitals. After a common development including deliverables, time-lines, Go / No Go, etc. we will continue to work with this company.

In fact, our product is not 'early': the therapeutic action is based on the laws of physics; as a result, it is quantitative (unlike products based on the laws of biology), can be modeled and can be predictive (unlike products based on the laws of biology); likewise, the development can be partly 'parallel' and non-sequential. In addition, for the same reasons, there is practically no "biological hazard" that stops the development of 90% of the molecules, and the probability of abandonment of the product under development by toxicity or inefficiency is much lower than for a drug, a molecule or a biological process.
Very similar nanoparticles as well as magnetic field gradients have been used for decades in patients without significant toxicity.
We will need a human prototype to reach a Phase I / IIa clinical study in patients with non-operable, non-metastatic pancreatic cancer. The total cost of development to reach the market, is estimated at 5 M €.

THE COMPANY

CC & C

Mr Barthélémy Brossel, CEO, PR, Social Network and Communication

Mr Rémy Brossel, CSO, MD, Medical Oncologist, Physicist

They are helped by a team: assistant: Christine Grau and Scientific Board composed of mathematicians, physicists, oncologists and entrepreneur in Health Facilities:

Daniel Gabay
Mathematician (Polytechnic), former director of research at CNRS

Jean-Marc Guinebertière
Pathologist (Institut Curie)

Stéphane David
Industrial manager (PhD, CEA)
Specialist in Electro-Magnetism

Christian Chillet
Researcher (PhD, CNRS / G2ELab)
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Medical device development specialist

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CELL CONSTRAINT & CANCER SA, founded in 2009, is a French company with a capital of € 395 075 governed by the laws and regulations in force.
CELL CONSTRAINT & CANCER SA belongs to private individuals.
The company is registered in the commercial register in Tarascon under number:
RCS 511-620-890 Tarascon
Creation date: 13 March 2009
The share capital is divided into 79,015 shares with a nominal value of € 5 each, fully paid.

TO WHOM?

Our first indication concerns locally advanced non-metastatic pancreatic cancers. The purpose of this first indication is to make operable non-operable pancreatic cancers operable. This concerns 30% of patients, or 120,000 patients per year.

Some data:
It's a growing cancer; now the fourth leading cause of cancer death, the second in 2030 if nothing is done.
This is an obvious 'unmet need' and a public health problem.

Obtaining an indication is done through a clinical study. The first clinical study is planned for locally advanced non-metastatic pancreatic cancer.
This PhI / IIa study is short-lived and requires few patients, therefore relatively inexpensive.

Treatment:
Intuitively, one can imagine a treatment 'radiotherapy-like', similar to radiotherapy but with an intravenous injection of nanoparticles before putting the patient on the treatment bed.

Figure 4

Turnover:

A machine of this type could have a price similar to a MRI system or a Pet Scan.
Consumables (nanoparticles vectorized on alpha v beta 3 integrins overexpressed in neovascularization) can be sold several thousand euros, with a large margin.

Development Strategy of Indications:

It concerns first cancer with few resources of treatment such as the pancreas and without development of new treatments (such as targeted therapies, immunotherapy) perceivable in the coming years.
At present the only indication of immunotherapy is marginal: pancreatic cancer with microsatellite instability, concerning very few patients.

The model: cancers for which few therapeutic solutions currently; no major predictable innovation; the locally advanced / metastatic cancer can be declined in many locations: bile ducts, primary liver cancer, glioblastoma (brain), rectum, esophagus, head and neck, stomach, bronchi, etc. In total, there may be a quarter of a million new patients in the United States that could be affected each year.
In the end, all the current failures, that is 10 million cancer deaths per year, may be affected.
The installation of this type of machine, country by country, takes time (authorization, environment, staff training, etc.) but the growth is rapid, as shown by the installation of MRI system in the 80s and closer to us Pet Scan.

COMPETITION

There is no direct competition in vivo. The methods used in vitro by Mr. Paszek (increase of the surface tension), or by F. Montel (increase in the osmotic pressure), etc., cannot be used in vivo.
We do not consider targeted therapies and immunotherapy as competing but as complementary. In fact, the targeted therapies are, from the point of view of cure, a failure (in solid tumor 3% of breast cancers, that's all) and we already see the limits of immunotherapy.
Immunotherapy is still in a research phase and may be the only indirect competition, but probably synergistic. At present the only indication of immunotherapy is marginal: pancreatic cancer with microsatellite instability, very few.

But the synergies with immunotherapies are emerging as shown in the recent article by A Miyazawa et al. Regulation of PD-L1 expression by matrix stiffness in lung cancer cells, 2018 (See also H Jiang et al. 2016).
In other words, the rigidity of the matrix influences the possibility of using immunotherapy.

MARKET

This is a highly regulated market. Class III medical devices are submitted to the health supervisory authorities. Note that in the US, the Food and Drug Administration has authority over drugs and medical devices.

Buyers are public and private hospitals in charge of cancer treatment, in France, public hospitals CHU or CH with an oncology service, non-profit private cancer centers and some private hospitals.

The magnetic field gradient generator is an heavy equipment.
The price can be estimated at about € 2 million with installation costs, training, maintenance... important.
Negotiations are long and the policy of installation of these innovative equipment follows a first exponential curve, then S before reaching a plateau of maturity / replacement in 6 to 8 years.
Six thousand hospitals active in the treatment of cancer with a complete technical platform are the primary targets over a period of 5 to 6 years. The consumable is per patient with a machine flow that could be of the order of 6 patients per day per machine.

THE ONCOLOGIC CONTEXT

Today's innovative drug therapies -targeted therapies- are developing slowly after the first spectacular results (imatinib, trastuzumab ...) and have cured only a very small number of patients at a huge cost, even though they have helped -marginally- to chronicize patients (breast cancer, colon ...). The current publications of academic or industrial origin offer interesting but modest improvements, therefore compatible with the addition of a mode of therapeutic action a priori independent actions on transduction-transcription-signaling cascades.

Immunotherapy has, for the moment, important limits: few sensitive patients, relapses, significant toxicities. The only cures are found in the rare tumors known to be manipulable by immunology: kidney, melanoma...

STATE OF THE ART OF INSTRUMENTATION

The magnetic field technique is a field of engineering science that has been mastered for a long time. Magnetic Particle Imaging (MPI) uses large gradients that are very well tolerated by the animal.

The passage of the animal to the human prototype requires the use of superconducting magnets.

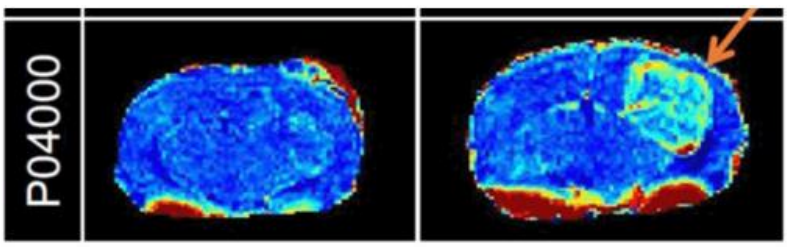
The proposed device is close to a MRI in the design, volume and cost of production. Budgets are difficult to assess today, as well as development time. However, and as a first approximation, we can consider that it will take two years to get a prototype to the dimensions of a patient.
An intermediate step is the construction of a model for rodents, used in the 'Proof of Efficacy', which will work on electromagnets, without drastic cooling, will modulate the amplitude and frequency and will begin the fields to work over distances in centimeters, so extrapolable to humans.

Feasibility studies on this device were presented at the American Association for Cancer Research in Boston in June 2016 (First meeting AACR devoted to 'Engineering of Physics of cancer').
http://actucancerpancreas.blogspot.fr/2016/05/abstract-qui-sera-presente-par-remy.html

An equipment for use in animals is being built in Grenoble, France.

Nanoparticles very similar to our product already exist. Designed to image neovascularization around the tumor, they allow to deposit a substantial amount of iron around the tumor itself. But these ferric nanoparticles used as MRI contrast agents have been a commercial failure and development was stopped. They are available for use in animals (Chematech, Dijon, France).

Figure 5



Anti-angiogenic treatment follow-up
R2* maps in a U87-bearing mouse model: specificity of P04000 as an αvβ3-specific imaging biomarker of angiogenesis.

These contrast agents have gone through preclinical procedure and therefore have a pharmaceutical file according to pharmaco-toxicological and clinical standards of the FDA and the EMA in Europe. Clinical toxicity is extremely modest, especially intravenously.

DEVELOPMENT STRATEGY

We see that the last stage of Research is the Evidence of In Vivo Effectiveness followed by the publication of an article in a scientific journal and presentation in meetings. The next step is the collaboration with manufacturers for the production of the human prototype and nanoparticle experimentation batches.

This will be followed by preclinical development: toxicology, CE / PMA markings and integrated phase I / IIa clinical trial.

To raise the necessary funds, private savings are no longer enough. A start-up that develops a breakthrough innovation has reduced access to public aid and is too risky for investment funds.

We are currently looking for investors and industrial partners. The preferential partners at this stage (seeding) are BAs able to aggregate around them a first round of the table to finish the research and to take the risk of a breakthrough innovation, so without a benchmark and with a rare expertise and outside Europe. But the capital increase remains the essential instrument.

An academic collaboration is underway for animal experimentation:

- With Stanford University (Ca)
- With the Faculty of Medicine of Bichat, Paris, in the frame of the FET Open (H2020) call.

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