FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA

A TECHNOLOGY TEASER

FLUORESCENT COLLOIDAL NANOCAPSULES

Released on July 2014

MATERIALS CHEMISTRY

Istituto Italiano di Tecnologia – Mission and History

The Foundation is intended to promote Italy's technological development and advanced education, consistent with national policies for scientific and technological development, thus strengthening the national production system.

For this purpose, the Foundation:

- helps and accelerates the development, within the national research system, of scientific and technological skills able to facilitate state of the art technological advancements of the national production system;

- develops innovative methods and know-how, in order to facilitate new high-level practices and positive competitive mechanisms in the field of national research;

- promotes and develops scientific and technological excellence, both directly, through its multi-disciplinary research laboratories, and indirectly, through a wide collaboration with national and international laboratories and research teams;

- carries out advanced training programs as a part of wider multi-disciplinary projects and programs;

- fosters a culture based on sharing and valuing results, to be used in order to improve production and for welfare-related purposes, both internally and in relation to the entire national research system;

- creates technological understanding about components, methods, processes and techniques to be used for the implementation and interconnection of innovative products and services, in strategic areas for the competitiveness of the national production system;

- pools research scientists operating in various research institutes and establishes cooperation agreements with high-level, specialized centers;

- promotes interactions between basic research and applied research facilities, encouraging experimental development;

- spreads transparent, merit-based selection mechanisms for research scientists and projects, in compliance with globally approved and established criteria.

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EXECUTIVE SUMMARY

The nanobeads described in this document can be functionalized with a variety of molecules for detecting specific biotargets and are easily dispersible in the interaction medium with cells or markers; therefore they can be used in a number of biomedical applications, such as bioimaging, bio and chemo sensing, cell tracking and sorting, bioseparation, drug delivery and therapy systems in nanomedicine.

The IIT technology consists in a method for the production of magnetic-fluorescent nanobeads (MFNBs) in a size range between 30 and 400 nm consisting of a few and simple synthetic steps, tuning both the total and the internal structure and size of the nanobeads by an easy control of the reaction parameters.

These technologies represent a unique chance for companies. IIT assets appear well positioned for an out-licensing strategy, providing the licensee partner with ability to take care of the late stage development, CE certification, scale-up and production process. The licensee should guarantee a high probability of market success based on consolidated marketing & distribution organization. A typical licensing strategy based on entry fee and subsequent royalties on net sales can be envisaged.

INTELLECTUAL PROPERTY

European Patent #	EP 2226634 – 21st October 2015
Priority Application #	IT 102009901710712 (TO2009A000169) – 6th March 2009
Applicant	Fondazione Istituto Italiano di Tecnologia
Inventors	Pellegrino Teresa, Di Corato Riccardo, Piacenza Philomena, Musarò Mariarosaria, Manna Liberato, Cingolani Roberto.
Title	Fluorescent colloidal nanocapsules, a process for their production and use in cells selection assays.

Short Description

This invention implements a new method of simultaneous detection and separation of biological entities like specific cells, based on magnetic nanobeads of strictly controlled size. The IIT Nanochemistry research group, has developed nanobeads made of aggregates of iron oxide nanoparticles enwrapped within an amphiphillic polymer to which oligothiophene fluorescents are grafted; their size is selectable in the range 30 to 400 nm. The nanobeds can be designed to exploit both a fluorescent and a magnetic effect, and can be used to target cancer cells. Thanks to the magnetic effect, they can be used to interact with the target and, because of the fluorescent properties, they can be used as reactor in the investigation process.

IIT TECHNOLOGY

The success of a therapy, in particular a cancer therapy, depends on multiple factors, among which an early and accurate diagnosis is fundamental. Often, the cancer lesion is identified only at an advanced stage of the disease, mainly due to the absence of a highly sensitive technique capable to detect low levels of tumor cells and/or markers in biological samples. Scientists are tackling this issue by reducing the probe size down to the nanoscale, which is expected to increase the detection sensitivity due to the higher surface to volume ratio. A nano-system designed for bio-separation must satisfy the basic requirement of being able to accumulate promptly via a magnet (so that a pre-accumulation step is possible), while its size must be small enough to ensure a high sensitivity. Also, it must be easily dispersible (soluble and stable) in the medium in which it has to be exploited and to interact with cells or markers. A system designed for multiplexing detection must additionally include code molecules (i.e. fluorophores) within its structure so as to be able to distinguish in parallel various analytes and/or tumor cells in the same biological sample. Up to now, multifunctional nano-tools able to perform simultaneous detection and separation tasks, have been based mainly on assemblies of magnetic nanoparticles and quantum dots. Albeit these nanostructures can be obtained with sizes smaller than 200 nm, their fabrication methods do not allow a systematic tuning of their dimensions down to a few tens of nanometers.

The IIT technology consists in a method for the production of magnetic-fluorescent nanobeads (MFNBs) in a size range between 30 and 400 nm consisting of a few and simple synthetic steps, tuning both the total and the internal structure and size of the nanobeads by an easy control of the reaction parameters.

The resulting nanobeads are based on aggregates of iron oxide nanoparticles (IONPs) enwrapped within an amphiphilic polymer to which oligothiophene fluorescents (OTFs) are grafted. MFNBs have both a rapid response to a magnet and a stable and tunable fluorescent signal for the presence of OTFs which have a high photochemical stability and structure-dependent emission spectra. Moreover, the process described doesn't involve separated and sequential steps of clustering of iron oxide nanoparticles and/or fluorescent coating of nanostructure.

Cell sorting experiments on KB tumor cells have shown the capability of the system in isolating cells in suspension within only 30 minutes, with a separation efficiency of nearly 100% (Figure 3a).

A complementary MTT test (a cell viability assay) performed to assess the citotoxicity of the MFNBs on KB tumor cell cultures, established it was less than 20% for iron concentrations equal to 16 µg/mL, while it reached 40% for the highest iron concentration (65 µg/mL) administered (Figure 3b), suggesting that on the isolated cells there is no need of detach the MFNBs since non-significant cell toxicity is observed. The uptake of the MFNBs was confirmed also via confocal imaging, by performing scans along the z axis of doped cells (Figure 3c and Figure 4), which showed clearly the localization of the beads within the cytoplasm into perinuclear vesicles.

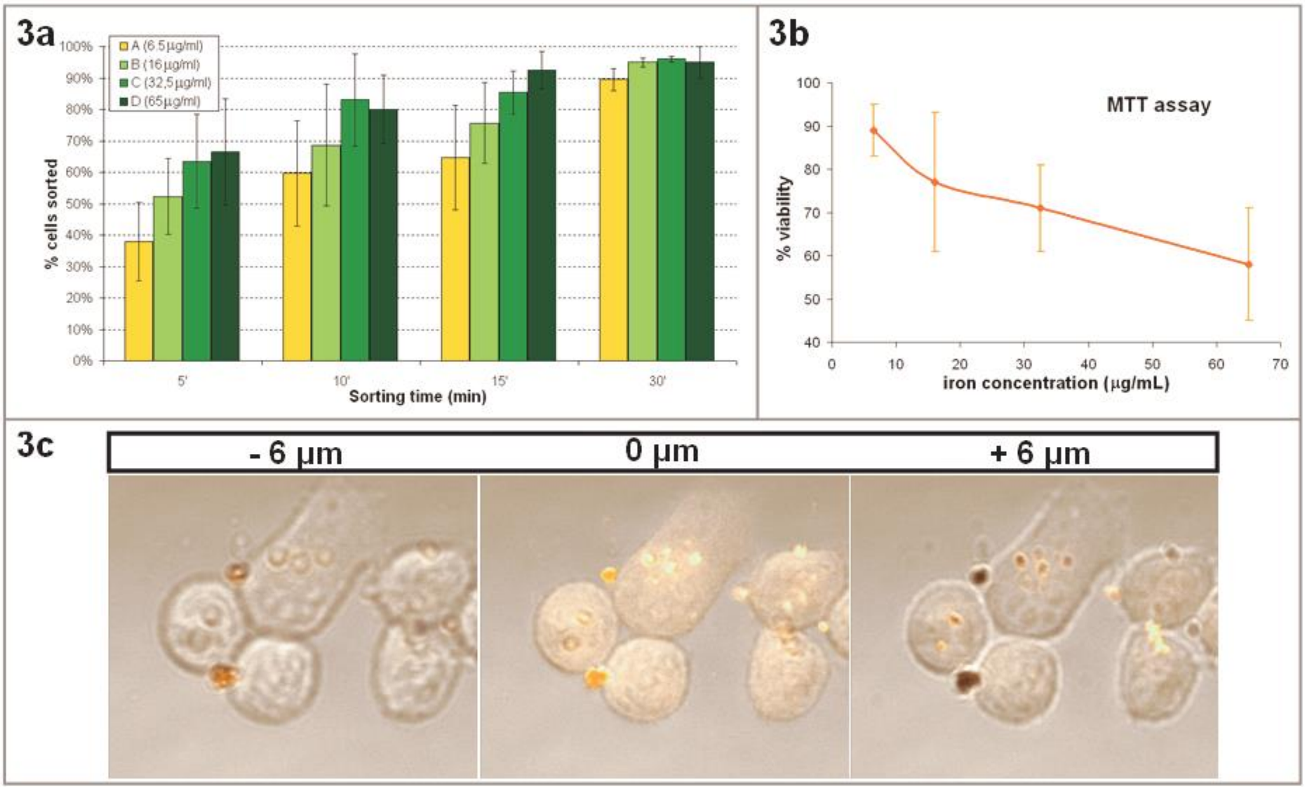

Figure 3. a). Results of cell sorting experiments. KB cells doped with three concentrations of MNBs (corresponding to 10, 16, 32.5 and 65 µg/mL of iron) were accumulated to the magnet at 5, 10 and 15 and 30 minutes. The cell counted are reported *vs* the time. **b).** Cell viability test on KB tumor cell cultures doped with increased amounts of MNBs. **c).** Sections of KB tumor cells doped with MFNBs based on OTF2.

Accordingly, the nanobeads are able to perform bio-detection and bio-separation tasks at the same time. Such a combination of magnetic and fluorescent properties in one entity makes magnetic and fluorescent inorganic nano-composite material able to be used in many biomedical applications, such as bio-imaging, cell sorting and bio-separation, diagnosis and, potentially, cell therapies as well as drug delivery systems.

The method according to the invention allows to obtain the following main advantages:

- Possibility of tuning the internal structure size of the nanobeads;
- Production of nanobeads in a wide size range (between 30 and 400 nm), compatible with bio-systems (cells or markers) and able to respond promptly to a magnet for bio-separation tasks;
- The process doesn't involve separated, sequential steps of clustering of magnetic nanoparticles to form a nanostructure and fluorescent coating of the nanostructure;
- High photostability is achieved as the polymer shell eliminates the risk of fluorescence quenching by the magnetic core;
- Low toxicity nanobeads and tunable fluorescent signal from OTFs are achieved;
- The method further allows to functionalize the nanobeads surface with a variety of molecules to detect specific bio-targets;
- The nanobeads have high stability and solubility in the biological medium.

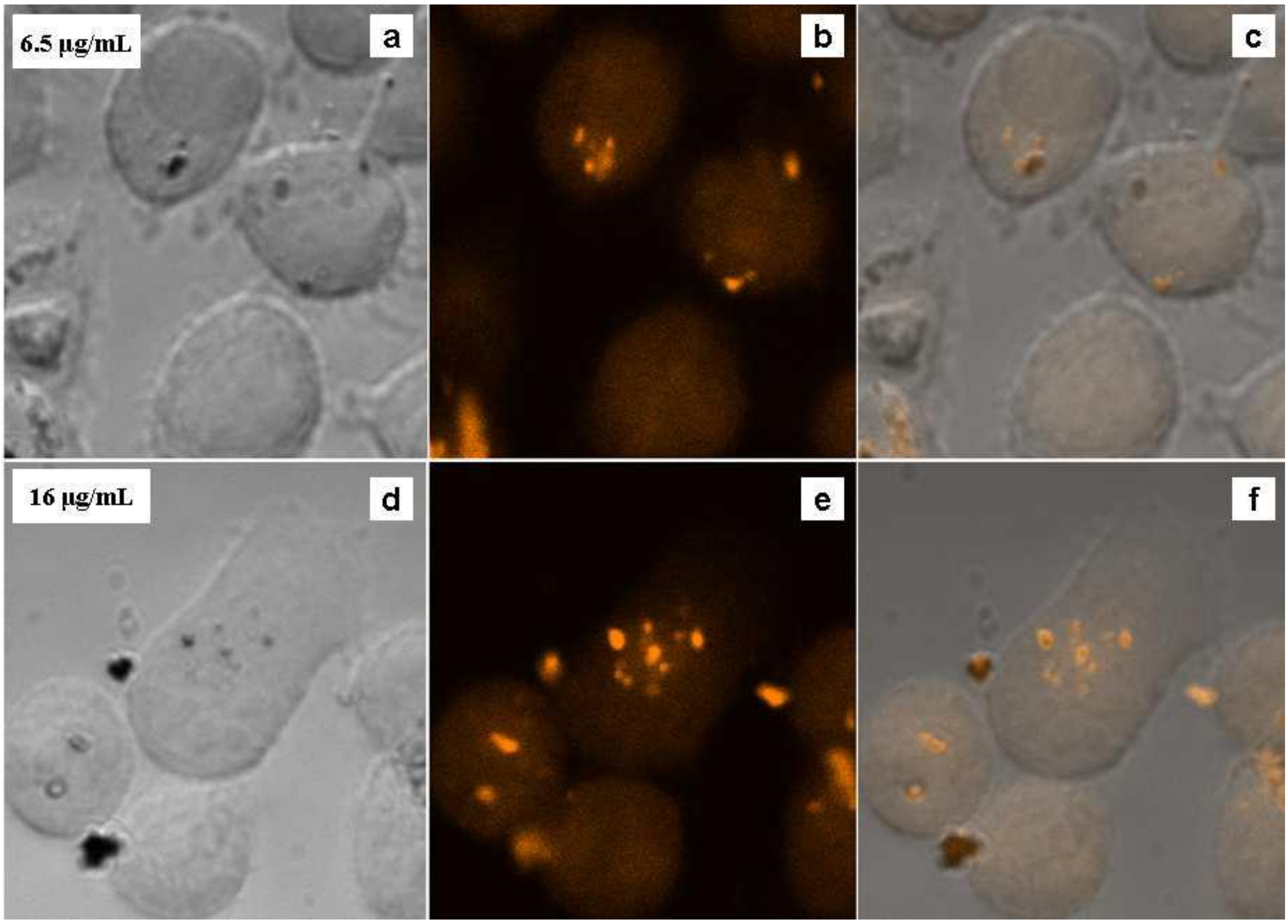

Figure 4. Confocal imaging of KB cells doped with two different concentrations of the MFNBs samples based on NHS-OTF2, namely 6.5 and 16 µg/mL (referred to the total concentration of iron). Panels **a** and **d** show the phase contrast images of the cells, panels **b** and **e** show the corresponding fluorescent image, panels **c** and **f** show a merging of the two pictures. In both cases the internalization of the MFNBs is clearly evident both in fluorescence due to the fluorescent spots recorded and in transmission image as shown by the dark spots on the cells.

MARKET ANALYSIS

Albeit mentioned by the inventors, the potential industrial application of the technology to assist in the drug delivery systems area does not appear sufficiently supported by the filed patent application, nor by internal IIT findings and associated literature. Accordingly, the market analysis has been focused on exploiting industrial applications for which robust data have been provided by the inventors and a clear market has been identified.

Based on the technology described in EP 2226634 A2, IIT internal documentation on the technology and related literature publications by the inventors and competitors, the cell sorting and separation technologies market has been analyzed for its current dimension and future trends through a web search-based retrieval of free-of-charge specific information.

Throughout the biological, medical, and pharmaceutical fields, cell sorting is used for research and some clinical practices. In research, cell sorting is already used to count, characterize, and analyze living cells and their particles. In clinical practices, it is mostly reserved for diagnostics, being therapy the next frontier. In principle, cell sorting could be used much more extensively, but the existing technologies, fluorescently activated cell sorting (FACS) and magnetically activated cell sorting (MACS), are expensive. Usually, cell sorting equipment is limited to a single laboratory within a large institution, such as a university, and that lab sorts cells for other researchers and clinicians.

In addition, the largest and fastest growing segment of the cell separator market is the aftermarket. Aftermarket products include magnetic bead kits, columns, tubes and reagents. Dynal Biotech and StemCell Technologies are the major magnetic bead suppliers.

If cell sorting cell equipment could become more commonly available, it could be make many applications such as the following more available and viable:

- **Biological research:** Identify and characterize cells and cell populations in complex systems in molecular biology, protein engineering, plant biology, and marine biology, and prepare pure sources of stem cells.
- **Drug discovery:** Isolate and grow living tissue for drug discovery experimentation.
- **Medical diagnostics:** Determine if there are cancer cells in a patient’s system (to head off cancer metastasis); precisely diagnose leukemia and lymphomas using blood plasma samples instead of bone marrow tests; analyze tissue specimens from patients; analyze human DNA and determine if there are risks for hereditary diseases.
- **Clinical practice:** Develop sources of purified cells to treat neurological degenerative diseases through transplantation; improve understanding of tumor immunology and treatment by evaluating pure samples of tumor cells; rescue healthy cells and re-introduce them into patients undergoing chemotherapy to reduce the side effects of chemotherapeutics.

Cell Sorting & Separation Technologies Market Size

According to a new market report published on May 2014 by the Transparency Market Research Group, “*Cell Separation Technologies Market (Technology: Gradient Centrifugation, MACS and FACS; Application: Stem Cell Research, Immunology, Neuroscience and Cancer Research) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019*”, the global cell separation technologies market was valued at

USD 1.7 billion in 2012 and is expected to grow at a compounded annual growth rate (CAGR) of 9.7% from 2013 to 2019, to reach an estimated value of USD 3.3 billion in 2019.

Cells play an important role in the field of microbiology, biotechnology and bioscience which have wide application in pharmaceuticals and healthcare industries. Taking into consideration the increasing demand for cell therapies to treat chronic diseases, research activities targeting cellular therapies have increased tremendously in the last decade. Growth in cell therapy oriented research & development has escalated the demand for cell separation technologies worldwide and is driving this market towards significant future growth.

The cell separation technologies marketplace is segmented on the basis of the technologies that are available and the application areas.

Cell Sorting & Separation Technologies Market by Technology

- Gradient centrifugation
- Separation based on surface markers
    - Magnetic activated cell sorting (MACS)
    - Fluorescence activated cell sorting (FACS)

From the very beginning of modern biology, cell separation from complex biological samples has always been a crucial issue. The progress made in immunology and stem cell technologies is entirely inconceivable without the preparation of homogeneous cell suspensions. In the early years, fractionation of blood cells by means of density gradient centrifugation was an important step ahead, soon followed by the sub-fractionation of lymphocytes into B- and T-cells when the discovery of CD antigens gave a new impetus to cellular immunology.

Nowadays, researchers have the equipment to separate subclasses of T cells and stem cells, e.g. by monoclonal antibodies against the surface antigens CD34 and CD133. The progress in recent immunology is strongly coupled to the development of sorting devices, mainly the fluorescence-activated cell sorter (FACS) which is a specialized type of flow cytometry. Individual cells are separated by electrostatic deflection in dependence on their light-scattering and/or fluorescent characteristics, which is a very elegant method but requires previous labeling of the cells with e.g. fluorogen-coupled antibodies. This can change the properties of the cell in terms of activation and metabolism. However, this is a common drawback in all sorting approaches where antibodies directly dock to the cells. The market leaders in fluorescence-activated cell sorters are, besides smaller suppliers, BD Biosciences and Beckmann Coulter.

In 1989, with the founding of the Miltenyi Biotec GmbH in Bergisch-Gladbach, Germany, a powerful company came up in the market of cell separation. The principle of their MACS technology (MACS = magnetic cell separation) was based on a very simple but efficient idea: magnetic microbeads are attached to monoclonal or polyclonal antibodies specific for a cellular membrane antigen. The incubation of a cell mixture with these beads results in a magnetic labeling of the targeted cells which then can be separated physically in a magnetic field. Using this technique, a cell suspension can likewise get depleted from a particular cell type - or different cell types in consecutive steps - which is called negative selection and which results in a homogeneous cell population.

Specific applications for magnetic cell separation systems include transfection, cell physiology, molecular biology, and genetic research. They are also used for microbiology applications such as pathogen detection in clinical, environmental and food labs. Although the FACS and the MACS technologies are widespread in biological laboratories, the search for alternatives that leave the targeted cells in a more unaffected state has continued.

Out of the various types of technologies available in the market, magnetic activated cell sorting (MACS) technology was the major technology segment in 2012, with market share of more than 42.5% in the global cell separation technologies market. Further, fluorescence activated cell sorting (FACS) technology is estimated to capture the market share of rest of the technology segments during the forecast period owing to increased adoption of fluorescence activated cell sorting technology into cell purity sensitive research areas. It is estimated that the global FACS market will reach USD 1,078.5 billion in 2019 growing at a CAGR of 13.9% from 2013 to 2019.

Cell Sorting & Separation Technologies Market by Application

- Stem cell research
- Immunology
- Neuroscience research
- Cancer research

The basic technology for cell separation hasn't changed much over the past several years. However recently these cells have been used for treating patients. As the promise of cell therapy is gradually realized, researchers are searching for cell separation technologies that can solve some basic problems, such as improving cell processing speed and making processing as sterile as possible. Researchers already use a mix of density-gradient separation, magnetic separation, and fluorescent flow cytometry to prepare cells for clinical use but hope for newer chip-based technologies to help advance the field.

Cell therapy has technically been around for decades - think for example to bone marrow transplants - but now researchers are finding more sophisticated ways to manipulate and use cells for medicine. Physicians and scientists are harvesting dendritic cells, T cells, stem cells, and more from patients' bodies and identifying and separating those with the strongest potential for helping patients. Once isolated, these cells can be grown in large quantity and returned to a patient's body to treat various diseases.

Though cell therapy remains a lively area of research, commercially available treatments have been slow to enter the clinic. The US Food and Drug Administration (FDA) approved the first-ever autologous cell therapy (which manipulates the patient's own cells and returns them to his or her body), Genzyme's Carticel, for treating damaged knee cartilage in 2007. The second approved cell therapy tretament, Dendreon’s Provenge, for metastatic prostate cancer, followed in 2010. Recently, the Centers for Medicare and Medicaid Services announced that it plans to cover this USD 93,000 prostate treatment, a major boost for Dendreon.

Allogeneic cell therapies, made from cells harvested from donors rather than the patient, offer the possibility of "off the shelf" use. Dozens of candidates are currently in clinical trials for applications ranging from boosting wound healing to treating graft-versus-host disease, to supplementing blood cancer chemotherapy treatments.

Because these cells are being used for medicinal purposes, the FDA regulates the entire process under the same rules that govern the production of pharmaceuticals, known as good manufacturing practice (GMP). Given the vast potential for cell therapy, many companies making instruments, reagents, and other tools for cell separation have shifted their focus away from the research lab into the translational and clinical research space.

However, researchers in the field say many gaps remain in what's available to develop clinically viable cell therapies, from instruments to antibodies. And because the payoffs so far have been relatively few and far between, some companies making these instruments or reagents have had to pull their products off the market, such as with Baxter's Isolex 300 Magnetic Cell Selection System.

Separating cells from their tissue of origin is one of the real bottlenecks for developing cell therapies for clinical use; while sorting cells out of blood is fairly easy, isolating them from fat - which has turned out to be a very rich source of stem cells - is another matter. Companies are putting a lot of effort towards developing simpler high volume, high throughput processes for separating cells from tissue. To this end, GE Healthcare Life Sciences offers the StemSource 900/MB Tissue Processing System, which was developed by Cytori Therapeutics. This sterile, closed centrifugation system can be used for extracting several different regenerative cell types from connective tissue. GE's Res-Q 60 Bone Marrow Concentration System, also centrifuge-based, can be used at the patient's bedside to isolate mononuclear cells from bone marrow in less than 20 minutes.

Islet cells can be separated out of pancreatic tissue using another popular centrifuge-based instrument, Caridian BCT's COBE 2991 Cell Processor. The instrument uses a closed fluid path and single-use disposable set for cell centrifugation - a vast improvement over traditional centrifuges - and conical tubes because it allows various fractions to be collected within a closed system.

Most researchers in the field use a combination of centrifugation, magnetic bead separation, and flow cytometry to develop their cell therapies. Magnetic separation has the advantage of speed, while cell sorting by flow cytometry allows for the use of multiple markers and results in a purer end product.

In the case of magnetic bead systems, a whole new series of reagents and equipment have been developed that allow for more automated processing and more closed operation in order to obtain a sterile cell product.

Miltenyi is about to introduce a second-generation version (named CliniMACS Prodigy) of the currently used instrument Miltenyi Biotec's CliniMACS platform, which uses magnetic-based technology for enriching target cells or depleting unwanted cells. This closed system can wash, separate (with density gradient cell separation or magnetic bead cell separation), and formulate the cells of interest, Schmitz explains.

Because companies are focused on making cell-sorting instrumentation and reagents that are suitable for use in clinical products, they are now thinking about how to comply with GMP-manufacturing guidelines. Maintaining the sterility of cell products is key; BD Biosciences, for example, offers a replaceable gamma-irradiated fluidics kit for the Influx cell-sorting platform.

It is thought that the ideal technology for producing cell therapeutics would be a speedier version of flow cytometry but there is the challenge of engineering a single-use fluid path that allows cell sorting under sterile conditions. Another possibility that researchers foresee is the use of microfluidics chips that sort cells via microscopic channels and gates that open and close to determine the cells' flow path. With several flow paths running in parallel on a single chip, the sorting process could be sped up considerably. What's more, the system could be entirely closed and aseptic.

Yet another advantage of electrostatic cell sorting on chips is that it would be "label-free." While centrifugation techniques are label-free also, both magnetic cell separation and flow cytometry require tagging cells of interest with antibodies or dyes, creating another challenge for researchers: finding ways to remove the labels such as using enzymes that can "clip off" antibodies after sorting or designing biodegradable labels that simply fall apart.

One factor delaying things, is the scarcity of antibodies that are made to GMP standards for magnetic cell separation. It is estimated that there is currently a dozen or so antibodies, made by BD Biosciences, Miltenyi, and other companies, that are suitable for preparing cells for clinical use. Yet, as with many other technologies related to the field, investors are shying away from such investments until they see some real success. However, investments in products that support cell therapy research is just as essential as the research itself.

Despite the challenges of developing commercially available cell therapies, more than a dozen companies have allogeneic or autologous products in various stages of clinical trials, including Geron, Osiris Therapeutics, Cytori Therapeutics and Aastrom Biosciences.

So far, large pharmaceutical companies seem to have held back from getting involved in cell therapeutics, which remains pretty much the province of startup biotechs and translational research institutions.

The Market for Circulating Tumor Cells (CTCs) and Cancer Stem Cells (CSCs)

Circulating tumor cells (CTCs) are believed to detach from primary or secondary tumors and enter the bloodstream, traveling to distant organs and forming new tumors. These cells that leave the primary tumor are able to colonize distant organs in the body and initiate the process of metastasis; however, their biology is still not entirely elucidated.

Circulating tumor cells have tremendous utility in cancer research, aiding scientists in deciphering the complex biology of cancer metastasis. Besides the applications in cancer research, the detection and analysis of circulating tumor cells has enormous potential in the diagnosis and management of cancer, as current tools, such as tumor tissue biopsy or imaging technologies, have numerous limitations. Despite their potential, the detection and analysis of circulating tumor cells has been a challenging endeavor, and their significance in cancer not completely understood. Progress in the field of CTCs-based cancer diagnostics and therapeutics has been thus far hampered by the rarity of these cells and the difficulty to isolate them from the patient’s blood. Nonetheless, in the past decade, numerous technological advances have contributed to a renewed interest in this field.

Kalorama Group has recently published a report illustrating the potential applications of CTCs in a variety of market segments, including Research, Prognosis, Diagnosis and Drug Development.

Cell Separation Technologies Market by Geography

Geographically, global cell separation technologies market has been segmented into four areas namely, North America, Europe, Asia-Pacific and Rest of the World. North America was the market leader in the global cell separation technologies market in 2012, mainly owing to availability of research funds, highly developed research infrastructure and higher rates of adoption of newer technologies in the practice. Further, growth of the North American cell separation technologies market is driven by factors such as technological advancement, higher healthcare spending and availability of supportive economy to conduct research. North America is followed by Europe.

COMPETITIVE SCENARIO

Leading Companies in the Cell Sorting & Separation Technologies Market

Some of the key market players include:

- Advanced Liquid Logic Inc. (USA, http://www.liquid-logic.com/)
- Baxter (USA, http://www.baxter.com/)
- BD Bioscience (USA, http://www.bd.com/)
- Beckmann Coulter (USA, https://www.beckmancoulter.com/)
- Cytori Therapeutics (USA, http://www.cytori.com/)
- EMD Millipore (USA, http://www.emdmillipore.com/US/en)
- GE Healthcare Life Sciences (USA, http://www.gelifesciences.com/)
- Guebert SA (France, http://www.guerbet.com/)
- Illumina Inc. (USA, http://www.illumina.com/)
- Invitrogen (USA, http://www.b2b.invitrogen.com/site/us/en/home.html)
- Life Technologies India (India, http://www.lifetechindia.com/)
- MagForce Nanotechnologies AG (Germany, http://www.magforce.de/en/home.html)
- Miltenyi Biotec GmbH (Germany, https://www.miltenyibiotec.com/en/)
- Owl Biomedical (USA, http://www.owlbiomedical.com/)
- PluriSelect GmbH (Germany, http://pluriselect.com/)
- Stemcell Technologies (Canada, http://www.stemcell.com/en/)
- Terumo BCT (USA, http://www.terumobct.com/)
- Thermo Fisher Scientific Inc. (USA, http://www.thermofisher.com/en/)

Leading Companies in the Circulating Tumor Cells (CTCs) and Cancer Stem Cells (CSCs) Market

The global market for CTCs detection, isolation and analysis devices is a heterogeneous and competitive market, constantly driven by technological innovation and demand for improved technologies. The market includes numerous competitors with different capabilities. These numerous specialized or research-based companies also develop and commercialize products for the detection, isolation and analysis of CTCs, and contribute considerably to the technological advancements in this field. As part of its coverage, Kalorama's report profiles several competitors in the market:

- AdnaGen AG (Germany, http://www.adnagen.com/)
- Advanced Cell Diagnostics Inc. (USA, http://www.acdbio.com/)
- ANGLE Plc (UK, http://www.angleplc.com/)
- ApoCell Inc. (USA, http://www.apocell.com/)
- Aviva Biosciences Corporation (USA, http://www.avivabio.com/)
- Biocept Inc. (USA, http://www.biocept.com/)
- Biofluidica (USA, http://www.biofluidica.com/)
- BioView Ltd. (USA, http://www.bioview.co.il/)
- Celula Inc. (USA, http://www.celula-inc.com/)
- Clearbridge Biomedics (Singapore, http://www.clearbridgebiomedics.com/)
- Creatv MicroTech Inc. (USA, http://www.creatvmicrotech.com/)

- Cynvenio Biosystems Inc. (USA, http://www.cynvenio.com/)
- CytoTrack ApS (Denmark, http://www.cytotrack.dk/)
- Epic Sciences (USA, http://www.epicsciences.com/)
- Fluidigm Corporation (USA, http://www.fluidigm.com/)
- Fluxion Biosciences Inc. (USA, http://fluxionbio.com/)
- Ikonisys Inc. (USA, http://www.ikonisys.com/)
- Janssen Diagnostic LLC (USA, http://www.janssendiagnostics.com/)
- Miltenyi Biotec GmbH (Germany, https://www.miltenyibiotec.com/en/)
- ScreenCell (France, http://www.screencell.com/)
- Silicon Biosystems (USA, http://www.siliconbiosystems.com/)
- Vitatex Inc. (USA, http://www.vitatex.com/)

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