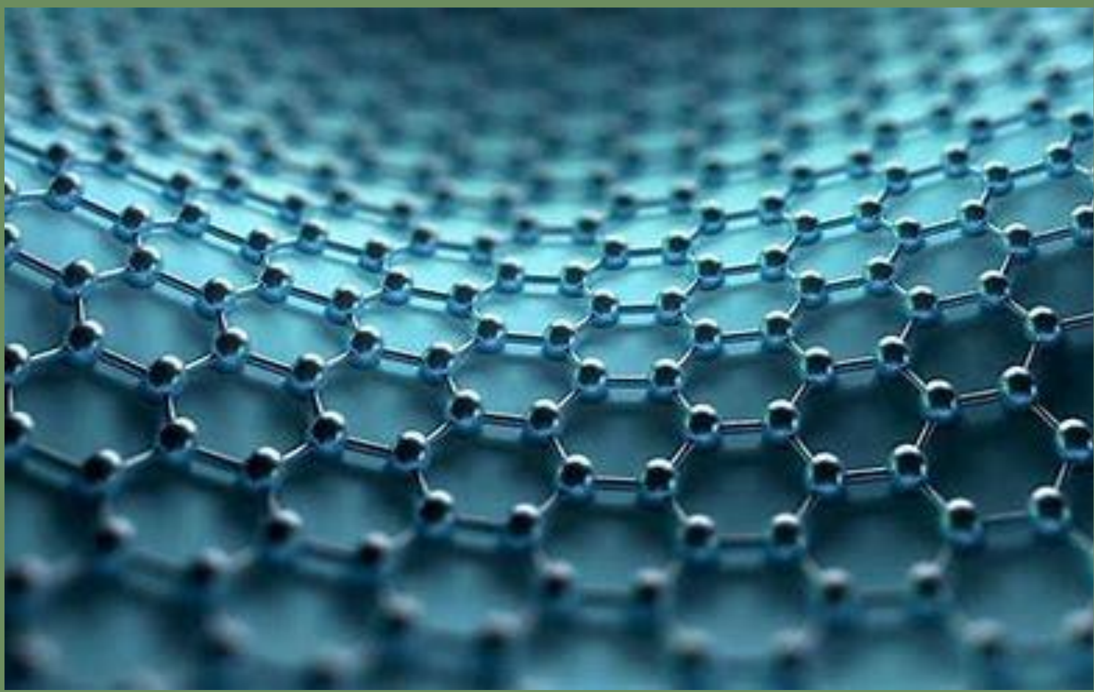

Roadmap for 2D Materials in Biotechnology

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Executive Summary

Graphene and other 2D materials have unique properties with potential to play an important role for medtech applications and biomedical applications. The promising biocompatibility, flexibility, and electrical conductivity are properties that can be utilized for sensors, electrodes, and implants.

2D material-based biosensors have progressively gained attention outside of the academic labs. Research results and early proofs of concept show that applications including sensors, smart membranes and antimicrobial surfaces are promising, and some European start-ups are already close to market with their products. Cancer treatment and neural interfaces are two promising examples where little has been done in Sweden.

The use of the antiviral and antimicrobial properties of the materials is still at an early stage. Graphene and graphene oxide show promising results for the use in biomedical devices, although further studies are needed to fully understand the materials' biocompatibility, and whether promising *in vitro* results really can be used for human treatment.

Despite the exciting technological progress, there is still a long way to go before biomedical devices or biomedicine with graphene or other 2D materials will be used in clinics. The biocompatibility is disputed among scientists, and more research on safety issues are needed. To users and producers of 2D materials, the value chain, including certification, testing, validation, and end users remains unclear. This is also true regarding the unique selling point, i.e., what differentiates a product containing at 2D material's solution from its competitors, in this case traditional methods.

We strongly recommend the establishment of a platform dedicated to advanced materials and their biotech/medtech/life science applications, with functions like stakeholder networking, technical due diligence analyses, interdisciplinary collaboration, and training. This should work in an international context. Furthermore, dedicated public funding should be allocated for collaboration within the platform.

The platform should strengthen collaboration between the established medtech/life science/biomedical companies, start-ups, and the material producers together with healthcare professionals, academia, and research institutes.

The focus areas could be (i) developing the right key performance indicators of the materials and products to **cut down access time to the market** (ii) **health and safety characterization**, (iii) **mechanistic understanding** of the interactions of 2D functionalized materials with biological systems, and (iv) **work performed in standardization committees.**

Contents

List of Acronyms

The acronyms that are described in the text are not listed here.

BioTech	Biotechnology is the integration of natural sciences and engineering sciences to achieve the application of organisms, cells, parts thereof and molecular analogues for products and services.
CVD	Chemical vapor deposition
Deeptech	A deeptech company is typically a startup company, providing technology solutions based on substantial scientific or engineering challenges.
GO	Graphene oxide
GR2M	Graphene and related 2D materials
Life Science	Branches of science that involve the scientific study of life – such as microorganisms, plants, and animals including human beings. In this report mainly drug formulation/effect, toxicology and human tissues/cells, tissue engineering and neural interface are of relevance.
Medtech	Medical Technology, also known as Health Technology accounts for technologies i.e. devices to the healthcare systems for diagnosis, patient care, treatment and improvement of a person’s health.
MXenes	A class of two-dimensional inorganic compounds consisting of atomically thin layers of transition metal carbides, nitrides, or carbonitrides.
PFAS	Per- and polyfluoroalkyl substances
rGO	Reduced graphene oxide
ROS	Reactive oxygen species
TRL	Technology readiness level
USP	Unique selling point

Introduction

Sweden is consistently ranked among the most prominent research nations in the world. The Swedish government invests significant resources in research and development, as this is a prerequisite to being a leading nation and reaping the benefits of contemporary globalization. Life science and advanced materials are two prioritized areas, and a combination of the two disciplines could place Sweden in the lead for the future.

Since the Nobel Prize in 2010, graphene and related 2D materials (GR2M) have passed their infancy and can now claim a rightful spot alongside more established material. This gives hope for an immense area of applications, including biotechnology, medtech and health care. But the road from lab to industrial use is long and winding and it can be a cumbersome trip for a small company to reach the market.

This roadmap has been developed in collaboration with stakeholders in academia and industry, aiming at strengthening research and development of biotechnology applications in Sweden related to 2D materials, and to accelerate future investments and collaborations. It identifies areas of strength and potential opportunities for Sweden, while also focusing on the challenges. Some recommendations on activities and measures needed to reach the visions for 2030 are included.

SIO Grafen is a national strategic innovation program with the aim to strengthen collaboration between academia, research institutes and industry regarding the production and use of graphene and other related materials. The program's vision is that Sweden in 2030 will be one of the world's ten leading countries in developing and using graphene and other 2D materials industrially**.** The long-term goals of SIO Grafen are defined as:

- Establishing 2D materials as a Swedish industrial area of strength.
- Creating a strong 2D material eco-system.
- Supporting complete value chains for graphene and other 2D materials.
- Ensuring that 2D materials are key enablers in the transition to a sustainable society.

The roadmap is the last in a series of roadmaps released from SIO Grafen. Previous roadmaps have focused on the areas of composites and coatings, electronics, energy, and manufacturing. All of these have mainly had a Swedish perspective, whereas this roadmap includes an international outlook.

Methods

For this roadmap, information for the analysis has been gathered using the following means:

Description of state of the art: The descriptions of state of the art were performed by researchers active in the field. It does not claim to be exhaustive, merely indicative.

Participation in meetings and workshops: The Roadmap and the related questionnaire were presented and discussed at Swedish Graphene Forum, in Sundsvall, November 2022 and at a NextBioForm project meeting in November 2022.

Identification of stakeholders: Relevant participants in SIO Grafen projects were identified as stakeholders. The project group collectively identified other relevant stakeholders among academia and large and small corporations, that either are working in the field with 2D materials or are working in the biotechnology area where 2D materials could prove useful.

Interviews: Stakeholders not known to already work with 2D materials were selected for interviews.

Questionnaire: A questionnaire was put designed by the project group and circulated through the communication channels of SIO Grafen (Newsletter and LinkedIn) as well as e-mailed to identified stakeholders.

Patent search: A search for patent families was performed from EP (European application), US (American applications) and WO (PCT applications). In addition, Sweden was added, as it is the focus of the roadmap.

Literature search: A literature search in Web of science has been performed based on combining “graphene or 2D material or 2D-material” with each one of the search terms “biomedical “, “diagnostics”, “antiviral”, “antimicrobial”, “biosensor” or “antibacterial “. The search was performed also for specific 2D materials other than graphene.

Review of other relevant Roadmaps: Several roadmaps and documents from Graphene Flagship, SIO Grafen and other sources listed in References at the end of this document, have been reviewed to get a picture of the areas of interest.

The Area and the Boundaries

2D materials are few-atoms-thick crystals or layered compounds with versatile mechanical, electronic, optical, and thermal properties. They include the graphene family of materials, and 2D versions of non-carbon materials such as molybdenum disulfide (MoS_2), tungsten disulfide (WS_2), hexagonal boron nitride (BN), and MXenes among others.

The discipline of biotechnology has applications in a multitude of areas, e. g. food technology, wastewater treatment, and environmental technology. This roadmap focuses mainly on medical and medtech applications.

Several applications can be found where 2D materials intersects with biotech/life science. This report focuses specifically on the following areas:

- Sensors, bioimaging and bioelectronics
- Printed electronics for biotech applications
- Smart membranes and surfaces
- Antimicrobial and antiviral surfaces
- Drug delivery and new therapeutics
- Bioengineering, including tissue engineering and regenerative medicine

The first part, *Current Status*, includes a survey of the technological state of the art regarding biotech/medtech applications of 2D-materials. This survey is followed by an overview of the development in Sweden over the last ten years, considering research funding, scientific publications, and patents. An international outlook, where market trends, health and safety issues, standardization and the regulatory framework are synoptically presented, concludes this part.

The second part, *Challenges and Opportunities*, covers two SWOT analyses, one for graphene/2D materials' area and one specifically for the development of sensors.

In the third part, *The Road Ahead* the vision beyond 2030, and recommendations with the purpose to bring usage of the intrinsic properties of graphene and 2DM's in biotechnical applications closer to the market are outlined.

Current Status

Scientific and Technological State of the Art

Medical, biotech and med tech applications can potentially be used in medical institutions to prevent, diagnose, monitor, treat and cure diseases. This chapter is a short overview of the scientific and technological progress and potential of the use of 2D materials in the designated areas.

Biosensors

According to the World Health Organization (WHO), one third of the global population is deprived of reliable access to needed medicines [1]. Among the leading causes of deaths worldwide is due to cancer and cardiovascular diseases. Tuberculosis is the world's second most deadly disease after HIV/AIDS. Diabetes is predicted to be the 7th leading cause of deaths by 2030.

Drug resistance, as well as incorrect, expensive, and time-consuming diagnostic tests, is currently outperforming disease control programs. In a nutshell, diagnostic tests need to be cheap, user-friendly, disposable, and reliable while maintaining high sensitivity and selectivity [2] [3].

Detecting reliable, multiple analytes in real biological samples such as blood, saliva and sweat using low cost, disposable and fast biosensor is a Holy Grail. With recent development, this can be envisaged. Traditionally, electrochemical, or organic transistors, Electrolyte-Insulator-Semiconductor (EIS), Ion-Sensitive Field Effect Transistors (ISFETs) etc. are widely explored for biosensing applications [4] [5].

Graphene is exceptionally conductive, highly stable in aqueous media and atomically thin. It can be used in electrolyte-gated graphene field effect transistors (EG-GFETs) [6], to detect variations in salt-concentrations, pH and type of ions present in an electrolyte. This can be used for detection of DNA hybridization, enzymes [7] [8], bacteria [9], pH levels of electrolytes [10], and ions [11] [12]. Furthermore, by modifying the surface chemistry of graphene, biosensors can be fabricated with long shelf-life and operate at ultra-low voltages [13]. These applications should serve as a springboard to leap into fast, highly stable, and sensitive multi-parametric 'all organic' biosensors based on graphene.

Sensors (biomedical imaging and diagnostic) and Bioelectronics

The exceptional biochemical sensing capability of 2D materials, due to their atomic-thin layer structure and large surface area properties, and their electrical conductivity can be altered as any particle or molecule in the vicinity of these 2D layered materials. In particular, the recent progress in the engineering of 2D materials via stacking, doping, functionalization, and alloying enables the design of even more complex structures. This development has contributed to promoting innovative ultra-sensitive and ultrafast response sensors for diagnostics and health-care applications.

There is an exponentially growing number of publications on the use of 2D material-based biosensors for detection of neurotransmitters (dopamine, serotonin, etc.), metabolites (glucose, lactose, ascorbic acid, adenosine, etc.), inflammation markers (reactive oxygen and nitrogen species, such as hydrogen peroxide and nitric oxide), proteins, nucleic acids, bacterial cells, and heavy metals [14]. It is worth noting that 2D material-based biosensors have been getting more and more attention outside of the academic labs. Excellent single or few-layer CVD graphene has for example been utilized to produce biosensors with good performance and low cost that benefited by the industrial-scale fabrication of the CVD graphene [15]. However, the functionalization of the 2D material surface, which has a significant impact on the optical, electronic, and vibrational properties, is an emerging research area for the community, even though it needs to be further investigated.

> " The French company Grapheal raised in 2021 1.9 M€ to proceed in the development of their graphene-based wearable patches, designed to allow the remote monitoring of chronic wounds. The company started to develop graphene-based sensors for SARS-CoV2, in collaboration with the University Hospital of Grenoble, they succeeded in developing a low-cost rapid saliva test for the virus." *(From Graphene Flagship Core Project 3, "Business Domain report – Biomedical applications")*

Printed Electronics for Biotechnology Applications

The ability to offer remote diagnostics in a cost effective, disposable form is steering the medical industry towards developing more products based on printed electronics. The low cost printed electronics device fabrication allows the healthcare industry to include disposable electrically functional parts. With higher reliability, the healthcare printed electronics products offer patients comfort and less invasive treatments.

Biosensors, such as blood sugar test strips, ECG sensors and pads for drug delivery, manufactured by using combinations of functional nanoparticle inks printed on thin film polyester, have become the attractive pathway for biomedical industries. Very recently, 2D materials have entered into a leading role here, being used as active materials or electrodes for such applications.

Printing as a manufacturing process brings the advantage that a wide range of substrates can be used, enabling e.g. flexible and stretchable printed electronics [16] [17] [18] [19] [20]. The same printing methods are available for 2D materials as well as for graphic or functional printing in general. These methods include screen, inkjet, gravure, and flexographic printing [16] [21] [22] [23].

Printed electronics is an attractive paradigm for realization of biotechnology applications. The large area of these systems makes printing a cost-efficient alternative [24]. Furthermore, since printing allows for easy integration of discrete materials on the same substrate through spatially specific deposition, printed electronics is particularly useful for integration of diverse biological functionality on the same substrate. By printed electronics technique, electrically functional inks can be deposited on the substrate, creating active or passive devices, such as thin film circuits, sensors, transistors, or resistors.

Smart Membranes and Surfaces

Smart Membranes

Smart membranes that respond to environmental stimuli are gaining attention because of their potential use in a variety of applications. The large interactive surface area of 2D materials allows for high 'loading' of actives. In some cases, e.g., in graphene, the electrical conductivity enables externally triggering release functionality. This concept is central to many applications such as skin-patches, gas and/or water purification membranes, etc.

Chemically tuning the surfaces in 2D materials with active sites, such as graphene oxides, reduced graphene oxides, or semiconductors such as MoS_2, allows possibilities to functionalize the materials to be selective to a wide range of molecules and ions (e.g., glucose, proteins, metal ions, etc.). In addition, the possibility of functionalizing or doping graphene with e.g., nitrogen, sulfur, fluorine, etc. also opens potential for selectively removing targeted molecules and ions. Recent advances in materials technology, especially of 2D materials, are very promising and have the potential to provide the critical breakthrough needed to revitalize the membrane technology [25].

Properties like exceptional mechanical strength, electrical and thermal transport properties, high surface area, and the wide range of possible surface chemistries [26], via doping [27] or functionalization are directly relevant for next generation membrane materials.

Due to the highly anisotropic and large interaction area of 2D materials, the percolation threshold for a dispersion of 2D materials is very low, easily forming an interconnected matrix, which can potentially trap and release active substances.

The inherent electrical conductivity, the possibility of externally controlling the capture or release rate and the possibility of monitoring the 'state-of-health' of such membranes via changes in electrical resistance due to changes in surface properties, makes it possible to develop 'smart' membranes that can predict time for filter change and/or perhaps even automatically trigger responses such as membrane regeneration.

Antimicrobial and Antiviral Surfaces

Antimicrobial Surfaces

Graphene and 2D materials have antimicrobial properties, which could be used in different biomedical and biotechnical applications. Several mechanisms contribute [28]:

Membrane Stress: the membrane stress consists of four actions: cut, insertion, pore formation and lipid extraction.

The sharp edges of GR2M flakes can cut bacterial membranes and cause leakage of intracellular material, causing bacterial death. For this mechanism the edge of the 2D material plays the important role. By the wrapping mechanism the GR2M can induce pores forming in the cell membrane, changing the osmotic pressure of the bacterial cell which then causes the bacteria to swell and die. Extraction of lipid molecules, due to strong dispersion interaction between graphene and lipid molecules, after insertion of the GR2M further adds to the membrane stress.

Oxidative Stress: ROS (Reactive Oxygen Species) produced by the oxidative stress of GR2Ms also contributes to bacterial inactivation through several mechanisms. The level of oxygen containing functional groups is important for this mechanism and GO (Graphene Oxide) generate more ROS than rGO (Reduced Graphene Oxide) and graphene.

The range of mechanisms show that different properties such as size, oxygen level, concentration in dispersion, and arrangement on a surface will affect the antimicrobial property.

The Graphene Flagship Roadmap focus report [29] in graphene based antimicrobial surfaces conclude that the GR2M are effective against multiple microbial species, have low cytotoxicity and very good biocompatibility. Importantly, the antimicrobial mode of action is mainly physical (e.g., membrane distortion), leading to low risk of antimicrobial resistance [30]. For GO, a time-dependent antimicrobial activity of has been shown, where the wrapping/trapping effect was observed to be a predominant antimicrobial behavior of GO against planktonic state bacteria, oxidative stress, and membrane stress associated with cell damage and leakage of intracellular content was found as an additional mechanism [31].

However, the mechanism on coated surfaces of the different GR2Ms, toxicity, biosafety and potential long-term release from surfaces still needs further investigation [29]. There is also a need for more detailed investigation of changes in molecular dynamics in the bacterial as well as mammalian cells up on exposure to GR2M modified surfaces. Furthermore, the actual *in vivo* antimicrobial performance and biocompatibility needs further attention [32].

Antiviral Surfaces

Antiviral applications have not gained as much interest as antimicrobial, as determined by the lower amounts of published articles (approx. 25 per cent in 2021 compared to antimicrobial, Scopus). Nevertheless, GO and its derivatives have wide-spectrum antiviral properties [33]. Similarly, to the antimicrobial properties of GR2M, the sharp edges play a role for GO and rGO inactivation of viruses, and subsequent outflow of intracellular metabolites [34]. Thus, these materials have potential in the development of antiviral surfaces and coatings.

Other Biomedical Applications

Neural Interfaces and Biocompatible Devices

> *" The Spanish company InBrain Neuroelectronics has advanced in the industrialization of nanoscale graphene electrode. They have entered a multi-year collaboration with Merck to develop the next generation of graphene bioelectronics for nerve therapies. Initial work will focus on inflammatory, metabolic and endocrinic disorders, using graphene for miniaturization, precision, and high modulation efficiency in the vagus nerve". (Graphene Flagship Core Project 3, "Business Domain report – Biomedical applications")*

In the past decades, a considerable effort has been made to develop new biomaterials that can be used in biomedical applications. In the field of neuroscience, monitoring of neuronal activities, leads to better understanding of brain functionality and eventually treating the neurological disorders. However, probing a neural tissue exerts specific limitations to the choice of the biomaterials. This is because in addition to biocompatibility, other properties should also be at place, naming high electrical conductivity, stability in long-term use, and specific mechanical integrity and softness. Having most of the above-mentioned properties, graphene and its derivatives have been recently used widely as substitute/addition to the available alternatives.

In this context, to detect the electrophysiological signals in the brain, graphene active sensor arrays [35] and linear graphene microtransistors [36] were shown to be able to reliably record and map the electrical activities in vivo. These new studies support the great potential of graphene's applications practically to detect and address neurological diseases such as epilepsy and depression. As a potent implantable probe, graphene has also been used in a variety of studies, where the conventional alternatives are lacking the ideal performance [37] [38] [39] [40] [41]. Lee. et. al., fabricated a new type of graphene oxide/polymer composite that possess significantly better electrochemical performances, while mechanical stiffness remained favorable for neuronal cells. This new composite was used later as substrate to grow and study neuron-like cells where it showed comparably better results in terms of protein expression and growth [42]. To hasten and support the healing process in the spinal cord injuries, Zhang et.al., made a new type of hydrogel consisting of cross-linked graphene oxide (GO) sheets with four-armed polyethylene glycol functionalized with an anti-inflammatory drug. This new material showed promising results in accelerating and guidance of new neuronal networks, due to high electrical conductivity of added GO [43].

Drug Delivery and New Therapeutics

The bioavailability of the drug/gene can be maximized due to efficient loading, target delivery, and controlled release by incorporating the therapeutics to suitable carriers. At the current state-of-art, graphene and related 2D materials are not commonly considered as drugs or therapeutics themselves, but mainly as drug delivery vehicles, as matrices for tissue engineered medicinal products etc.

Following the successful use of carbon nano tubes in lab experiments (CNTs) for drug/gene delivery, graphene sharing a similar chemical structure with CNTs, can also be used as drug/gene delivery carrier. Currently, cancer therapy is discussed as one of the potential areas of graphene, especially for delivery of combined drugs. The latter is very interesting for cancer therapy and personalized medicine - two fields with increasing relevance and importance.

Due to the specific features of graphene, the numerous chemical strategies and the abundant chemical functions, especially graphene oxide (GO) attracts great interest as novel drug/gene delivery system with high efficiency, multi-targeted drug delivery and controlled release [44]. Major arguments for graphene are the possibility of a targeted delivery and the delivery of a set of combined drugs. Therefore, it can be assumed that graphene will get a major weight in the nano drug delivery market due to these specific advantages. However, just like for CNTs, material characterization, in turn, is a key element of hazard assessment to determine the structure–activity relationship, and extrapolation should be avoided [45].

Further potentials for the use of graphene/GO in cancer therapy are phototherapy and enhancement of drug efficiency through photo-enhancement. In phototherapy, heat generated by light absorption in graphene induces thermal destruction of cancer cells containing significant concentrations of graphene. [44] [46]. The scientific results in this context are very promising, but they are still in the stage of mouse models. The photothermal effect of graphene could be also used for enhancing the efficiency of chemotherapeutical drugs such as DOX (Doxorubicin). [44] When photothermal therapy is combined with a photosensitizer an alternative therapeutic modality called photodynamic therapy can be developed/achieved. The results of scientific research in this context are promising, but it is still too early to make relevant market estimates.

In addition, different 2D materials beyond graphene including MXenes, 2D metal-organic frameworks (MOFs), and covalent-organic-frameworks (COFs), are examined as potential drug delivery systems [47]. Specifically, the surface-modified and drug-loaded MXene nanosheets by soybean phospholipid (SP) were investigated as a stimuli-responsive drug-releasing system upon external irradiation of change in pH [48]. It was observed that synergistic chemotherapy of the drug loaded MXene nanosheets which were triggered by laser irradiation resulted in the complete elimination of tumors. However, the same delivery system could only inhibit the growth of tumor tissue partially without the application of laser irradiation [48]. In addition to MXene nanosheets, the 2D MOFs were used for loading of 4,4'-(1,2-diphenylvinyl)-1,2-di-(phenylcarboxylic acid) (TCPE) and doxorubicin for imaging and drug delivery, respectively; and also, for pH-controlled ibuprofen release [49] [50].

Bioengineering (including tissue engineering and regenerative medicine)
Various authors have described the use of GO or rGO as scaffolds in tissue engineering [44]. The whole field of tissue engineering is a dynamic area of modern medicine, and graphene will bring in new prospects. For instance, substrates from stem cell differentiation or components for implant devices can be generated. Tissue regeneration in the nervous area appears to be very promising.

Although the field is promising, it should be said that it is still in an early exploratory stage. For the whole field of tissue engineering a relevant number of Transnational Patents were registered in recent years, but in smaller numbers than for prostheses or small implants. Thus, the market is relevant, but quite specialized.

Sweden, Development 2010-2021

"In the intersection between the traditional research areas, completely new technology will thrive. This, in turn, becomes the basis for the highly technological industry of the future."

The quote is from Sweden´s major weekly magazine on technology, Ny Teknik in June 2002, where the journalist Anders Wallerius explained what impact nanotechnology would have on the industry´s development on a twenty year's horizon. Thanks to the long-term national research programs founded in the beginning of the century, e.g., *Materialkonsortier (SOU 1998:128 Samverkan mellan universitet och högskolor och samhället i övrigt*, Sweden) is still at the forefront in materials´ research as well as in the biotech field in Europe.

The Graphene Flagship (2013-2023) is led by Chalmers University of technology includes nearly 170 academic and industrial partners in 22 countries together and strengthens Sweden's position in the 2D material area.

Since 2014, innovations on graphene and 2D materials have got a kick-start in Sweden via the strategic innovation programme SIO Grafen, which has established an ecosystem composed of the best material researchers, companies, and entrepreneurs in the country. The following chapter deals with this development during the last decade, from lab benches to business.

Research Funding

Since 2009 until 2022, 443 MSEK has been allocated via public funding to research on graphene and 2D materials, generally. Vinnova, together with Formas and the Swedish Energy Agency are the main sources for this funding via SIO Grafen. The Swedish Research Council has granted a few projects directly coupled to 2D materials in biotechnology.

Vinnova has via SIO Grafen financed graphene projects in different phases (pre-studies, research projects, demonstrator projects) with a total of 206 MSEK during 2014-2022, 157 MSEK of that in open calls. Given the specific conditions from Vinnova of a certain grade of co-financing from industry, the total economic engagement in these graphene projects is much higher, 370 MSEK.

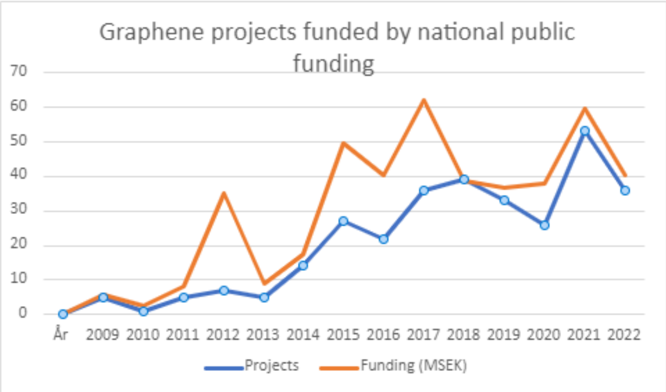

Figure 1 The number and amount of public funding in MSEK during the time period 2008-2022. (swecris.se). During this period, 309 projects have been funded for a total amount of 443 MSEK. This includes the funding of SIO Grafen's program office and internal projects. Not included in the graph is the industry co-financing of Vinnova projects.

To date, only five per cent of the SIO Grafen projects have been designated to the biotechnological field. The granted projects have so far been focusing on antibacterial surfaces and electrodes, and on occupational health and safety issues.

The Knut and Alice Wallenberg foundation (KAW) recently launched a new research program – Wallenberg Initiative Material Science for Sustainability (WISE), to which the foundation is allocating 2,7 BSEK during the period 2022 – 2033. There is no budget within WISE specifically for graphene in life science. However, if the technologies match any of the initiative´s thematic areas, namely energy, circular materials replacing rare, energy-intensive, and harmful materials, or materials for sustainable technologies and applications, they might be right for WISE funding.

In an international context, the European Commission (EC) has been funding 2D biotechnology research, mainly via the Graphene Flagship over a period of ten years (2013-2023). The total budget for the Flagship, including activities in Horizon Europe and member state contributions will be in the range of 1 B€. However, the biotechnology is only one of several application areas in the Flagship and its share of the Flagship budget from the EC to date is roughly estimated to 20 M€. The focus within the biotech/biomedicine arena is mainly on graphene-based biosensors and neural interfaces. With an additional 20M€ investment, the European Commission has recently funded the creation of an experimental pilot line for graphene-based electronics, optoelectronics, and sensors [51].

Scientific Publications

A literature search using Web of Science was performed November 2022. It combined "graphene or 2D material" with each one of the search terms "biomedical", "diagnostics", "antiviral", "antimicrobial", "biosensor," or "antibacterial". In total, in the range of 10 000 publications were found. Analysis of geographical distribution of publications always involve uncertainties as many documents involve researchers from different countries.

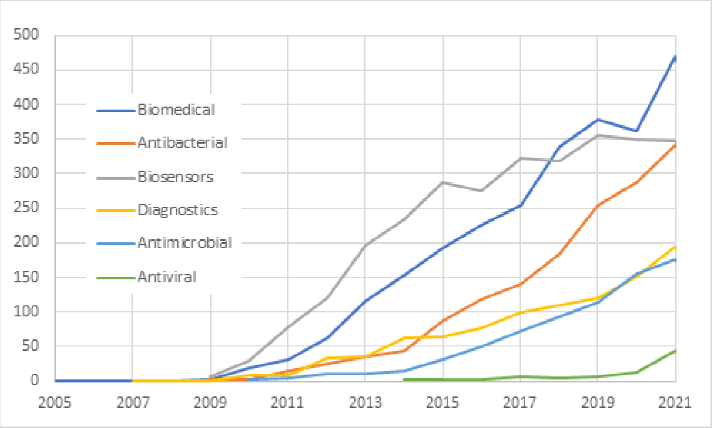

Figure 2 The number of publications per year for the period for combinations of "graphene or 2D material or 2D-material" and each of the six search terms "biomedical ", "diagnostics", "antiviral", "antimicrobial", "biosensor" and "antibacterial," respectively. Search for specific 2D materials other than graphene did not give any additional publications. (Web of Science)

It stands clear that China is by far the most active country in the field (active in appr. 40 per cent of the publications) followed by India and USA (active in appr. 12 per cent of the publications, respectively). The most active European country is United Kingdom (active in appr. 3 per cent of the publications). Sweden appears around place 30 (active in less than one per cent of the publications).

The Mijakovic lab, with activity in Gothenburg (Chalmers) and in Copenhagen (Technical University of Denmark, DTU) is the most productive one in Sweden. It is led by Professor Ivan Mijakovic at Chalmers and involves more than 30 researchers, with Santosh Pandit driving the efforts in using graphene for antimicrobial coatings, drug delivery, and sensing of bacterial cells. Furthermore, the activities cover development of advanced graphene-based antibacterial coatings, to be implemented onto various surfaces of medical and industrial relevance.

Patents

A patent evaluation has been performed for graphene and other 2D materials in biotech applications. The Swedish activities were evaluated by searching for Swedish organizations among the assignees of the search results. Out of 640 patent families (defined as all patent applications/patents that origin from the same priority document) in the area smart membranes, biosensors, and drug delivery, only three had Swedish assignees. All these three targeted biosensor applications. Without weighing the graphene-relevance of these three patent families, it can be concluded that based on the search results of the patent evaluation, 0.6 per cent of the number of patent families have Swedish assignees.

The search resulted in zero patent families for smart membranes and drug delivery and three patent families for biosensors. Only in one of these patent families is graphene a central part of the invention. A search in the European Patent Office's database on graphene in general reveal that only a small number of Swedish companies have filed patent applications, mainly regarding material production.

When comparing the outcome of the patent evaluation to the "The Graphene Flagship Technology and Innovation" from 2014, we can observe that for the period 2014-2022, the number of novel patent applications for the area increased quickly around 2015. Until 2014, the patent activities were dominated by USA and Europe. The Asian activities, primarily in China, Japan and India, have increased rapidly after 2014.

Companies

To our knowledge, Swedish industrial activity regarding the use of 2D materials in the biotechnology field is very low. Three graphene suppliers and five pharmaceutical/medtech companies have so far participated in research projects financed by SIO Grafen. The applications included different sensor technologies, antibacterial surfaces for catheters and dental implants, and cancer detection.

Swedish startups with focus on graphene and7or other 2D materials listed as partners at SIO Grafen are 2DFab AB, Bright Day Graphene AB, Grafren AB, Graphensic AB, Graphmatech AB, Smena AB, Tenutec AB and Smart High Tech AB. Other partners that have been involved in the SIO Grafen biotech/medtech projects are Sahlgrenska University Hospital, Wellspect HealthCare, Alfa Laval, Dentsply IH AB, Astra Tech, Astra Zeneca, LunaLEC, Lund University, Umeå University and Chalmers.

So far, no Swedish research results in this area have reached the market.

Research Centra, Available Infrastructure and Business Support

Research on biomedical applications of 2D materials is performed at many different university sites in Sweden. In this section, we showcase the activities at Chalmers University of Technology, Karolinska Institutet, and RISE, respectively.

The **Graphene Centre at Chalmers** with gathers all research at Chalmers University of technology on atomically thin 2D materials (including graphene, transition metal dichalcogenides, van der Waals heterostructures and related materials). One of the areas is exploiting the optimal surface-to-volume ratio to design highly sensitive biosensors and explore the possibility to apply 2D materials as antibacterial coatings.

2D-TECH (2D material-based technology for industrial applications) is a Vinnova competence center hosted at Chalmers. The vision is to establish an internationally visible and competitive Swedish hub for excellent 2D materials research and technological innovation. Within the biotechnology area they have so far been focusing on developing antibacterial graphene-polymer composite surfaces.

The **Institute of Environmental Medicine** at Karolinska Institutet has a strong international dimension, with participation in international research consortia funded by the European Commission, including the Graphene Flagship. The work on 2D materials focuses on the elucidation of mechanisms underlying toxicity with a particular focus on hazardous effects on the immune system.

At **RISE**, current research on 2D materials is performed on sensors and smart membranes, with capabilities also in drug delivery, neural interfaces, antimicrobial surfaces and toxicology.

Available infrastructure, testbeds

Below is a list of available infrastructures and testbeds.

SIO Grafen's compilation of test beds of use for 2D material, arranged according to application areas of which biotechnology is one https://siografen.se/om-sio-grafen/2d-material/testbaddar/

SciLife labs is a national infrastructure in the area of biomedicine www.scilifelab.se.

There are also numerous testbeds available for use of 2D materials in biotechnology at **RISE** (www.ri.se), some of which have extensive experience in 2D materials such as: Surface analysis and surface design, Sensors, and sensor systems, Printed electronics arena. There are also other testbeds which can become useful when developing 2D material applications in the biotechnology area: Design, modification and formulation of pharmaceuticals and medtech products, Antimicrobial materials, Surfaces and coatings, Biological safety and function, 3D bioprinting and Additive manufacturing.

Myfab offers services within micro and nano fabrication through the partner nodes at Chalmers, KTH, RISE and Uppsala University (www.myfab.se).

European Network of Pilot Production Facilities (www.eppnetwork.com/), gathers stakeholders regarding framework, characterization, standardization, health, and circular economy. Incomplete, but still useful.

Trade organizations like Swedish Medtech, SwedenBio, Läkemedelsindustri-föreningen, IKEM, NanoMedNorth and others can play an important role in finding partners, potential collaborators, as well as business support and information.

Biotech and Life Science in Sweden, from a Deeptech Perspective

For a well-functioning environment for deeptech startups, support of academia, capital investment and established enterprises is required. This section refers to a recent report published by Vinnova [52].

Life Science [52]

When looking at the research and innovation environment in Sweden in general (not specifically focusing on 2D materials), life science is an area of academic strength, with a high number of scientific publications when comparing to other regions (Great Britain, The Netherlands, South Korea, Massachusetts, California, Canada, Germany, Israel and Schweiz). The publications are of good quality and are cited over the average for these regions. The academic centers are listed by publications in the area: Karolinska Institute, Uppsala University, Lund University, Gothenburg University, Karolinska University Hospital, Sahlgrenska Academy and Umeå University. Life science also has the largest number of established enterprises and most start-ups compared to other areas of strength within deeptech in Sweden. There are also some strong companies, when it comes to patenting AstraZeneca, Essity Hygiene & health, Raysearch Laboratories, Mölnlycke Health Care are in the lead.

Health Care and Biotechnology are the two most common areas for start-ups in the life sciences, followed by pharmaceuticals, medical devices, medical and health diagnostics.

Industrial Biotechnology and advanced materials [52]

In the area of industrial biotechnology and advanced materials, Sweden is highly ranked, compared to the regions mentioned above. The patents are of good quality as they are often cited. There is a significant overlap with life science as many of the technologies can be used in both industrial as well as life science applications. As for publications KTH Royal Institute of Technology has most patents, followed by Chalmers University of Technology, Uppsala University, Lund University, Luleå University of Technology and Stockholm University in the area of industrial biotechnology and advanced materials.

Nanotechnology is the most common area for start-ups, followed by biotechnology and health care.

International Outlook

Trend Analyses

The Graphene Flagship has produced several Roadmaps including one for Biomedical applications [53], which stated that generally the following application areas of graphene in biomedicine prove to be relevant: Drug/gene delivery especially cancer therapy, Bioimaging & Biosensing, Antibacterial materials, Biocompatible devices including prostheses, bioelectronic medicine, small implants, tissue engineering, and finally Neural interfaces.

In addition, wearables for consumer lifestyle health monitoring are covered in the Graphene Flagship Roadmap for Electronics & Photonics [54]. Furthermore, in vitro diagnostics, point of care testing (POCT) and biosensors are covered in the Sensors chapter [54]. Antibacterial materials and coatings that are also of interest to prostheses or for biocompatible devices are covered more broadly in the Grafen Flagship Road map for Composites, Bulk Applications and Coatings [55].

Their conclusions were the following:

Sensors
Europe is a strong player in sensors and there is an innovative and strong basis in Europe that could take up graphene inventions and innovations. The market attractiveness for biosensors is high and they can be used in many different applications.

Antimicrobial and Antiviral Surfaces
Regardless of tremendous commercial opportunities for graphene-based antimicrobial surfaces, most GRMs-based applications still remain in a research phase. A major general challenge is the availability of material with stable quality and purity, according to appropriate standards. Antimicrobial surfaces within healthcare facilities were identified as the single most urgent issue.

Experts clearly identified a need for stronger coordination and collaboration throughout the entire value chain to identify the most promising application areas including an urgent need for increased interdisciplinary interaction between different disciplines to integrate molecular science with engineering.

Neural Interfaces
For neural interfaces, there is a window of opportunity for novel and improved graphene-based devices and technologies to offer innovative and more efficient solutions. The lack of sufficient capacity to provide innovative neural interface devices for medical evaluation was identified as the single most important bottleneck.

> *"Recently, our Work Package also discovered the potential of graphene to sooth anxiety – inhibiting the negative effects of post traumatic stress disorder. In a model study, injecting graphene oxide into a specific region of the brain silenced the neurons responsible for anxious behaviour. Tested in mice, this work provides another great demonstration of the therapeutic potential of graphene."*
> www.grapheneflagship.org

Drug Delivery
Drug delivery systems using graphene are at early stages and thus there are insufficient experiences as to advantages and disadvantages. A potential barrier to the application of graphene in drug/gene delivery is the safety issue. However, major arguments for graphene are the possibilities of targeted delivery and the delivery of a set of combined drugs. The potential of getting access to a large market for cancer therapy is very high, as any promising method of improving the results of cancer therapy will be adopted rapidly.

Tissue Engineering
Tissue regeneration in the nervous area appears to be very promising. The market is relevant, but quite specialized.

Implants
2D materials as coating material of prostheses could be an interesting application, as the market is very promising. Performance in comparison to competing materials

such as special steel or ceramics will be important for the breakthrough of graphene-based solutions.

Patents

A patent evaluation regarding graphene and other 2D materials for biotechnology utilization has been made, based upon dividing the patents and patent applications into three main categories: C1. Smart membranes, C2. Biosensors and C3. Drug delivery. For each category, several search words have been used in combination with graphene and other relevant 2D materials, see Table 1.

A patent family is defined as all patent applications/patents that origin from the same priority document. To reduce the search results to the most relevant patent families, the search has been limited to documents from EP (European application), US (American applications) and WO (PCT applications). In addition, Sweden was added as it is the focus of the roadmap. National patent applications/patents from e.g., China, India and other Asian countries are not visible in the search results.

The search has been made for the period 2002-2022. The numbers for 2021 and 2022 are not yet accurate since documents are published up to 18 months after submission.

Table 1 The search words for the three categories C1-C3.

	C1. Smart membranes	**C2. Biosensors**	**C3. Drug delivery***
2D material search words	graphene	graphene	graphene
	boron nitride	MXene	
Search words for the categories	smart membrane	biomedical	mRNA delivery
	patches	biosensor	gene therapy
	antimicrobials	wearable sensor	cancer therapy
	gas adsorption	point of care diagnostics	pDNA
	gas separation	diagnostic sensor	siRNA
	metal ion removal	therapeutic sensor	
	removal organics from water	glucose sensor	
	PFAS	electrochemical sensor	

*mRNA (Messenger RNA), *pDNA (Plasmid DNA), siRNA (Small interfering RNA, short interfering RNA, silencing RNA)*

Evaluation Results

Comparison between the Three Categories

In Table 2, an overview of the distribution of patent families for the three respective categorized are shown. 72 per cent of the patent families (464 out of 640) are categorized as C2 Biosensors, whereas the remaining part is equally distributed between C1 Smart membranes and C3 Drug delivery. Table 3 shows the relation between active and abandoned applications for all three categories.

Table 2 The number of patent families and validated patents for the three categories C1-C3.

	C1. Smart membranes	C2. Biosensors	C3. Drug delivery	Total
Patent families	79	464	97	640
Validated patents	157	967	171	1 295
Applications	488	2 660	518	3 666
Total	724	4 091	786	

Table 3 The relation between active and abandoned patent applications for category C1-C3.

Category	Alive applications	Abandoned applications
C1. Smart membranes	62.9 %	37.1 %
C2. Biosensors	71.1 %	28.9 %
C3: Drug delivery	74.5 %	25.5 %

Category C1. Smart Membranes

There is no organization dominating this field. No organization with more than three patent families have been identified. Out of the search terms, “antimicrobial” is strongly dominating.

As can be seen in Figure 3, the number of novel applications/years have been rather stable over the period. The geographical distribution (Figure 4) of applications shows a rather proportional distribution between the main actors Europe, Asia (China and Japan) and USA.

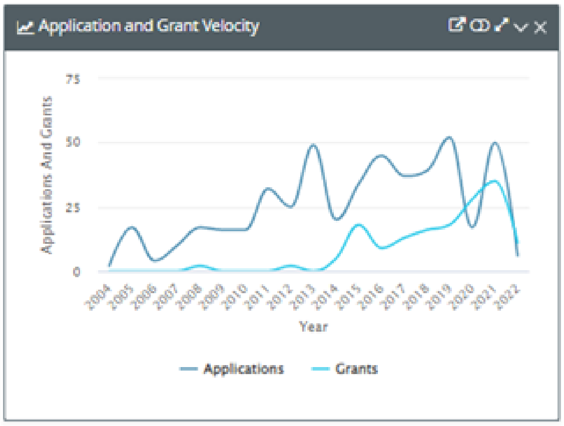

Figure 3 The number of novel patent applications/ year and granted patents for years for C1

Figure 4 Illustration of the geographical distribution of applications in C1

Category C2. Biosensors

Even though organizations like University of California, Nokia, MIT and Samsung are highlighted in the search results, their number of patent families is in the range of 5-10 per organization. Hence, there is no organization dominating the field. Out of the search terms, “electrochemical sensor” is strongly dominating. The number of novel applications per year had a peak in 2018 (Figure 5). The geographical distribution of applications in Figure 6 shows strong American activities.

Graphene is a central part of the invention as shown by Claim 1 of US2021116408: "An electrode for an electrochemical device, the electrochemical device capable of detecting a biological target in a sample, wherein at least part of a surface of the electrode is attached with a graphene-polypyrrole based composite, and wherein the graphene-polypyrrole based composite is attached with at least one biological targeting moiety."

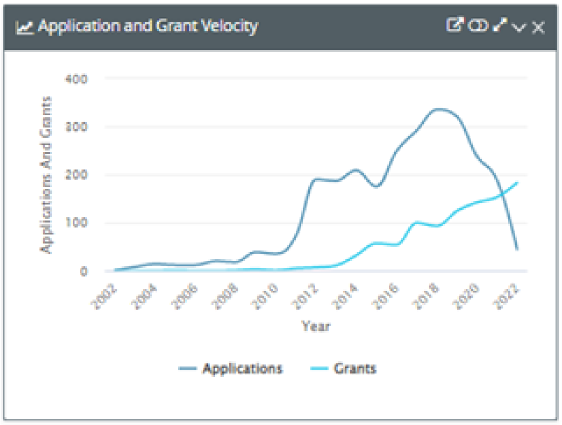

Figure 5 The number of novel patent applications/year and granted patents for years for C2.

Figure 6 Illustration of the geographical distribution of applications in C2.

Category C3. Drug Delivery

There is no organization or company that is a major stakeholder in drug delivery. No organization has been identified with more than five patent families. Out of the search terms, "delivery" is the most common.

As can be seen in Figure 7, the number of novel applications/years peaked in 2016. The geographical distribution of applications in Figure 8 shows strong American activities.

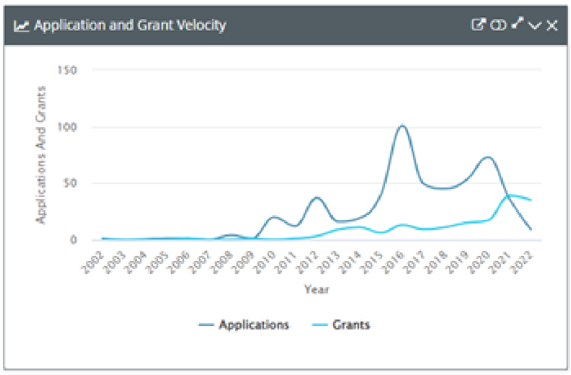

Figure 7 The number of novel patent applications/year and granted patents for years for C3.

Figure 8 Illustration of the geographical distribution of applications in C3.

International Centres of Excellence

Cambridge Graphene Centre and Graphene Engineering Innovation Centre, Manchester, UK: These are two centers with a lot of research and innovation on graphene in the UK. Neither of these has biotechnology as a priority area, however at Cambridge work is performed om sensors and bioelectronics.

International Iberian Nanotechnology Laboratory, Portugal: The 2D Materials and Devices research group focuses on CVD growth, transfer, and device fabrication, using 2D materials, clean-room technology, and Raman imaging for structural characterization. Particular attention is given to biosensing devices, where immuno-assays and DNA sensors based on graphene liquid-gate FETs were developed. The device's specificity for biomarkers is achieved by functionalizing the graphene channel. Attomolar DNA detection based on electrochemical arrays of graphene microsensors is achieved. In the framework of the project NeuralGRAB funded by "La Caixa" Foundation, they collaborate with the University of Minho Medical School and the Madrid Astrobiology Center to achieve brain activity recording of a panel of neurotransmitters (Dopamine, GABA, Glutamate) with physiological spatiotemporal resolution using multiplexed graphene transistor platforms.

GraphCAT, Spain: A hub, hosted by Istituto Català di Nanociencia y Nanotecnologia (ICN2), that brings together diverse members of the graphene ecosystem in Catalonia. Members are non-profit research centers. The vision is to establish Catalonia as an international reference in graphene research, development, and innovation, with multiple local industries deriving strong competitive advantage in the global marketplace through the integration of proprietary graphene technologies into their products and services. It will also provide support for the transfer of technology to industry, as well as the creation of spin-off companies. Projects for biomedical devices focus mainly on sensor applications related to the monitoring, and stimulation of the activity of the central and peripheral nervous system.

Aachen Graphene & 2D-Materials Center, Germany: A research center with a focus on bridging the gap between fundamental science and applications within graphene and related materials-based electronics and photonics. The center will aim to enable the integration of the already ongoing work from RWTH Aachen University and AMO GmbH under a legal framework that allows for full collaboration between the groups. In particular, the center will focus on addressing the challenges of future technology including high-frequency electronics, flexible electronics, energy-efficient sensing, photonics with graphene and related materials and their heterostructures.

Graphene Research Center, South Korea: Hosted by the Advanced Institute of Convergence Technology, this research center focuses on application of graphene and 2D materials to biotechnology. The center highlights work on novel approaches in detecting and treating neurodegenerative diseases, various protein-based regression diseases, and vision-related diseases.

Market and Market Trends

The health market has a large volume and is quite independent of economic crises. Nevertheless, it has very specific structures which make access difficult. For a medical product from research to first launch, it can take 13 years, or more. Research-intensive medical products and devices are in general only profitable if they reach the global market.

There is not yet a unique market accounting for graphene biomedical applications, as the market segments vary depending on the type of graphene technology and the way it is used. Very few technologies have so far been launched in very niched segments. It is therefore not possible to have a clear definition and size of the market of 2D materials in healthcare application.

The Graphene Flagship's technology and Innovation Roadmap (TIR) is a guide of the market and industrial needs and the opportunities and challenges for graphene technologies. The Fraunhofer Institute is leading the work. According to a recent update of the TIR, biosensors might be on the market in a few years' time. Regarding neural interfaces, devices for clinical usage could be ready and market-approved before 2030. In the fields of drug delivery and bioelectronics medicine, most technologies are still at low TRL levels and will need several years of development before products are found on the market.

Several requirements need to be met for a successful market entry. Bottlenecks, like production capacity and reproducibility must be resolved. Access to dedicated small pilot lines may resolve this situation.

Many potential applications compete with conventional solutions, which can be both fast and cheap. One example is the antimicrobial surfaces arena. Only if graphene-based approaches can provide specific advantages, they will succeed to establish themselves in the marketplace. Also, creation of legitimacy is important and can be met by early diffusion of knowledge, to and between the different stakeholders.

Safety Aspects

Safety assessment is an integral part of the innovation process, and material characterization, in turn, is a key element of hazard assessment. Safe and sustainable by design is therefore a key approach for innovation. For biomedical and related applications, biocompatibility is crucial as well as other health and environmental effects of the specific material. The effects may vary as a function of the materials' intrinsic properties. Despite exciting technological progress in many areas, there is still a long way to go before applying graphene and related 2D materials as biomedicine or biomedical devices in clinic.

In June 2022, The EU Observatory for Nanomaterials (EUON) released a study on potential health and environmental effects of graphene and related two-dimensional materials. The study, which is based on a review of ten years of publications in the field concludes that cytotoxic effects have been identified for graphene and 2D materials. It recommends that, when health and/or environmental risks are reported, doses and exposure scenarios should be considered for manipulation and use [56].

It further states that more knowledge is needed, especially regarding the ecotoxicity of graphene-based materials. The authors also found that a precise description of the materials used often were lacking, a fact that makes it difficult to draw specific conclusions. This was also the conclusion of a systematic literature review studying 93 papers studying a total of 185 GR2M. They observed that the lack of proper physicochemical characterization made it difficult to establish conclusive structure/activity relationships between different GR2Ms and cytotoxicity, oxidative stress etc [57]. Therefore, complying to standards and/or OECD Test Guidelines is crucial in this respect [56]. The inclusion of graphene as a representative industrial nanomaterial in a custom-designed material library for testing the toxicity and the creation of a specific reference library of well characterized GR2M will be fundamental for benchmarking purposes in basic and regulatory research [45].

Other studies claim that fundamental obstacle is the biosafety concern of 2D materials. The controversy related to biosafety of the materials needs to be cleared to pave the way for biomedical applications [58]. It has been demonstrated that the cellular toxicity of commercial graphene products is not related to a particular characteristic of graphene; rather, it is fundamentally determined by the presence of impurities in the commercially available graphene family materials tested [59].

The molecular mechanisms of how GR2Ms interact with major components on biological membranes are summarized in a review by Chen et al, and some general guidelines for modulating the biological performance of GMs in the area of antibacterial activity and cancer therapy are proposed. They concluded that further investigation of molecular mechanisms with strict standards for quality evaluation of GR2Ms and methodologies used in subsequent biological experiments. are needed in the field of biomedical applications [58].

The Regulatory Framework

To place a product on the market one must comply with the regulatory requirements in force. The applicable law in force is based on EU-regulation and focuses on the safety of patients and healthcare personnel. Apart from the regulatory frameworks REACH and CLP, which apply to chemicals production, two specific frameworks apply to biomedical and medtech products.

Medicinal Products Regulation (MPR)
Generally, medicinal products are drugs, i.e., small chemical molecules or biopharmaceuticals, such as antibodies or therapeutic proteins. Advanced therapies such as tissue engineered products, cell therapies etc. are covered by the definition. The key points of this regulation, with relevance for 2D materials at the present state of development, are that all medicines offered for sale in the EU must have prior authorization from either a national authority or the European Medicines Agency, EMA. Manufacturers must provide a range of detailed therapeutic information about the product, including any possible side-effects. If a medicine’s risk-benefit ratio is

not considered favorable or its therapeutic effect is insufficiently substantiated, authorization may be refused.

Medical Devices Regulation (MDR)
The Medical Devices Regulation is considered as a national law in all EU member states. It aims to ensure that medical technology products and services used in healthcare and by the patient themselves are safe and effective. The rules provide clarity both regarding what is expected of the manufacturer and of the products, as well as what the responsibility looks like during use.
Medical devices comprise a very diverse set of products. Most of the potential applications of graphene and related 2D materials in the health sector are medical devices for in vivo or in vitro use, like medical implants or prostheses equipped with coatings or sensors for in vivo use. Diagnostic devices like labs on chip for point-of-care diagnostics, wearable electronics with graphene-based sensors for monitoring purposes also falls under this definition.

In contrast to the MPR, which lays out product specifications in detail, the MDR approach gives quite general basic requirements. The task of defining detailed technical specifications is delegated to the standardization bodies. If products conform with European standards, it is assumed that they are safe and are thus marketable in all EU member states.

Characterization and Standardization

Industrial utilization and, thus, sales of graphene increase substantially. However, there is a slow lowering of production cost and reduction will remain limited until substantial volume expansion is achieved. Furthermore, the marketing and sales highly depend on quality and consistency of graphene products [29].

For proper quality control and hazard assessment, the materials need to be well-characterized using standardized and validated characterization techniques. Given the variety of available 2D materials, a description of the physicochemical properties must be provided in all toxicological and pharmacological studies. However, at present standards are being developed for chemical and physical characteristics of GR2M. However, it will be a few years still before these are all published. A Technical specification on ISO/PWI 9651 Nanotechnologies – Classification framework for commercial graphene-related 2D materials is also underway.

Standards can accelerate the commercialization, as they combine knowledge and perspectives from different stakeholders. They also support industry and where applicable encourage harmonization across regulators. Both graphene producers and users increasingly recognize the importance of standards to support the uptake and diffusion of GRMs in antimicrobial surfaces development [29].

As far as we know, there are no specific standards for 2D materials in the biotechnology application areas yet. At the ISO (International Organization for Standardization) conference in November 2022, there was a presentation discussing the need of standards for nanomedicine. However, it is plausible that this will initially focus on liposomes, and lipid nanoparticles, rather than 2D materials, as liposomes constitutes 50 per cent, and the "others" category where 2D materials may be included constitutes of 5per cent of the > 50 formulations currently on the market and >400 in clinical trials. Furthermore, there is already an ASTM E56.08 –Nano-enabled medical products which lipid composition, polyethylene glycol quantification and lipid nano particle characterization are included.

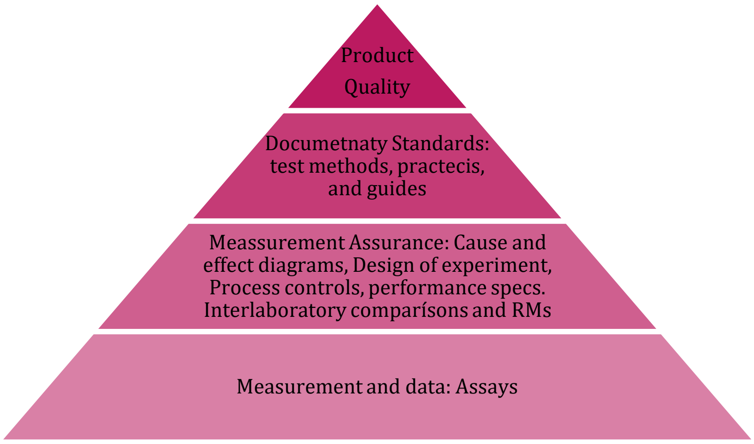

Figure 9 Hierarchical diagram of the role of different standards in the nano-medicine area [60].

Challenges and Opportunities

Small Players' Dilemmas

Every industrialist understands that regulations are there for a reason, and that there is no market without data. However, the specific regulations may pose challenges to startup companies, since those who fail to comply to the regulatory frameworks risk losing the right to place their products on the market in the EU. For a small company, this may be seen as a cumbersome process that consumes a great number of resources.

On the other hand, start-ups that bring innovations to the health care market are in a good position, since only highly profitable projects receive support in the long run [61].

Financial Challenges

The current major global financial downturn is causing challenges for startups and SMEs in general, especially those that do not yet have any products on the market. For many investors and venture capitalists, this downturn has led to that they are moving away from early startups, and instead are focusing on companies that already are profitable or are close to the market with their product offerings.

Capital, when available to these companies, has also become more expensive. This means that the market value of the companies raising money has decreased substantially, which in turn means that the existing shareholders face a situation where their current share of the company is at risk.

Challenges Raised in the Questionnaire

A questionnaire was sent out to stakeholders in academia and industry with the purpose of getting an instant snapshot of the challenges and opportunities they see in their daily business. The questionnaire was followed up by interviews. Out of the eleven respondents, seven were conducting research, two were performing research/feasibility studies. Two respondents had not used 2D materials at all yet.

The materials' superior properties, e. g. thermal, electrical, mechanical, and optic properties were mentioned as the **value-added features**. The high conductivity, high transparency and the processability was also appreciated. The antimicrobial nature, large surface area, and the ease of functionalization could pave significant impact on drug delivery and biomedical sensors.

Regarding **challenges**, the respondents highlighted issues like materials availability and cost, quality, possible toxicity, sustainability, and the lack of a sustainable supply-chain. These answers came from respondents that were using 2D materials at some level.

Other challenges that the stakeholders faced were the selectivity and sensitivity for biomedical sensors. The long-term performance of surface coatings in biomedical applications has not yet been investigated by the respondents. Another perceived obstacle was to get organizations to understand the innovation ecosystem and how each organization contributes to it.

Among the main challenges encountered during development were the understanding of the mechanism of 2D material synthesis, the mechanistic understanding of antimicrobial surfaces and dispersion. Upscaling might be costly, and handling of dry powders may cause a problem in the process.

The value chain, including certification, testing, validation, and end users remained unclear. The support given from SIO Grafen is highly appreciated, especially the meetings and seminars, which provides opportunities for networking and finding collaborative partners. Further help could be in the areas of networking with profile deep tech investors and potential customers and corporates.

SWOT Analyses

The Swedish 2D materials community is well prepared to tackle some of the hurdles to gain market shares in biotech/med tech applications, thanks to traditional strongholds in both disciplines. The weaknesses, displayed below can somewhat be dealt with, and threats can be avoided. In the SWOTs (Figure 10) analyses below, some of these circumstances are listed.

Table 4 shows a SWOT analysis for the entire field of biotech 2D material-applications. Since there is a lot of activity especially regarding sensors, this area is analysed in detail in a separate SWOT, see Table 5

Figure 10 Schematic SWOT analysis. This photo has an unknown author and is licensed according with CC BY-SA

Table 4 SWOT for 2D material applications in biotechnology, Sweden

Strengths	**Opportunities**
• Strong academic and industrial knowledge base in materials science and graphene. • Strong knowledge base in life science. • Sweden has an open and inclusive discussion climate where different stakeholders can meet. • Internationally recognized as leading, both in life science and graphene. • High ranking in the European EECO Innovation Index. • Advanced materials/2D materials regarded as drivers for sustainability by the European Commission. • Strong national network of stakeholders within the graphene community.	• New regulations could imply harder restrictions on traditional materials which are harmful to health and environment. This could create a window of opportunity for 2D materials if proven less harmful. • The sustainability of graphene could be improved by using biomaterials. • Graphene has several mechanical properties suitable for neural interfaces, a hitherto underdeveloped application area. • Participation in Horizon Europe projects and European network initiatives could ameliorate engagement, collaboration, and visibility. • Global networking among research peers, especially in USA and Asia, is a low hanging fruit. • Securing the value chains is a long-term opportunity. • Available consortia collaboration could ease the burden of REACH legislations
Weaknesses	**Threats**
• Low TRL within biotech for 2D materials. The change to 2D material may be seen as a difficult and insecure step "Why change a winning concept?" Lack of USPs for most applications. • Relevant companies are few, small, and have low sales numbers. The large companies are awaiting technology maturity, in particular when it comes to health and safety. • Low incentive in companies for using advanced materials. Sceptic attitude to 2D materials by life science corporations. Low driving force towards "the unknown". • Lack of commercial critical mass. Underdeveloped value chains (e.g., a need for quality-controlled 2D materials for biomedical products). Low level of collaboration between Swedish universities. • Immature area concerning certified 2D materials, their quality and health effects. • Weak interdisciplinary collaboration (materials-AI-biotech/med tech)	• Increased competition from other antimicrobial materials/solutions, as well as from other carbon-based materials, some of which are already on the market. Is there room for graphene-based alternatives? • Long time to market for biomedical products in general. • Many health care professionals' express scepticism towards new technology. • Unknown presence of 2D materials in Vinnova's upcoming Impact Innovation programs. • Swedish start-ups tend to be acquired by international corporations as soon as they show the slightest progress. Low return on innovation investment.

Table 5 SWOT for graphene sensors and other 2D sensors in Sweden

Strengths	**Opportunities**
• Graphene has unique properties that are advantageous for sensors (biocompatible, low cost, etc). • Strong academic knowledge on graphene/2D materials-based sensor technology for life science applications • Good infrastructure (sensor design tools, simulation/modelling competence and sensor fabrication facilities), e.g., open support demo/test beds in institutes and universities, as well as the MyFab cleanroom network. • Rich academic experience in related fields such as nanotechnology, photonics, and electronics that help to promote graphene sensor innovations including possible new IPs and advanced know-how. • Strong collaboration academia-industry for sensors through earlier SIO Grafen projects. • Strong national network of stakeholders within the graphene community.	• Strong need of sensors in biomedical fields, such as diagnosis, for both in vitro and in vivo scenarios. • Eagerness from clinical and academic researchers to collaborate. • Several EU programs have applications/projects offering funds/network to develop graphene-based sensors for a wide range of needs. • Possibility to spin off start-ups to produce sensors utilizing the graphene and 2D materials.
Weaknesses	**Threats**
• Standardization and regulation for medical use of biosensors still lacking. • Still a long time until common use in clinical environment. • Lack of knowledge regarding use of the sensors *in vivo,* especially the sensor packaging is still underdeveloped. • Interdisciplinary collaboration is underdeveloped, despite good ambitions. • Lack of financial opportunities for low TRL projects. • No critical mass of human resources in the field.	• Long time to market for biomedical products in general. • Fierce international competition.

The Road Ahead

Areas of Strength for Future Competitiveness

The life science sector in Sweden is quite significant. According to statistics from the trade organizations SwedenBio and Swedish Medtech, there are around 800 companies, out of which more than 600 companies are active in the medtech business. In 2019, the government launched a national Life Science strategy, which provides an opportunity for consensus and cooperation. It states, among other things, that Sweden is aiming to be a leading Life Science nation. The Swedish government has made large investments in infrastructure to support life science research for several years, both in academia and industry.

New materials, like 2D materials and the graphene family, will play an essential role as enablers for future health technologies. This includes digital technologies in health, in our response to today's health threats and even more so in the future. The use of artificial intelligence (AI) will be a useful tool to improve materials, processes, and design of future medical devices. Being at the forefront in materials science and staying open for cross-sectoral collaboration will therefore be of utmost importance.

The future of healthcare will be based on quick and personalized diagnosis, more and more ambulatory interventions, personalized treatments, and a wide range of regenerative medicine.

A Strong Knowledge Base

Sweden has a strong knowledge-based capacity in material science, biochemistry, and biology. Getting developments to market is however challenging for companies, due to the cost involved in product certification, the lack of suitable standards and suitable collaborations between low TRL players, industry, and clinicians.

Deploying innovations and new technology in the health sector can be difficult, due to political and financial reasons, among others. The trade organization Swedish Medtech is trying to overcome these hurdles in close collaboration with four regions in Sweden. The project *Innovation Engine* targets better knowledge and increased understanding between the medical device industry and healthcare. It will create new forms of collaboration to achieve a functioning implementation process of new technology.

Roads Less Travelled

Biomedical and med tech applications of 2D materials will reach maturation, however, the timeline will probably be somewhat stretched beyond 2030 for applications like drug delivery and antibacterial surfaces on prostheses. Sensors in different forms (wearables, monitoring etc.) will reach the market at an earlier stage.

Due to the increasing resistance to antibiotics of some bacteria, there is a high demand for surfaces with antibacterial, antiviral and antifungal properties.

According to the findings in the patent section (page 19), this seems to be an emerging area, not yet fully exploited and could therefore be an opportunity for Swedish stakeholders.

Other applications for functional materials, including 2D materials, are wearable devices for health and biomedical applications. Giant international companies, like Apple Inc., are already active in this segment, but there could be room for new and sustainable innovations.

The Swedish company LunaLEC has for example developed a liquid light concept, the Light-Emitting Electrochemical Cell (LEC). The planar structure in which the light-emitting organic layer is sandwiched between two conductive electrodes, makes it suitable for integration into devices where it can conform to specific dimensions, and still emit light from the entire surface. Possible applications may be in medtech devices for skin diseases.

Today, European research remains scattered both thematically and geographically, and this is also a problem in Sweden. The scarcity of resources (funding and device availability) demands a prioritization of efforts to accumulate critical mass to push an innovation towards the medical market.

The need for better collaboration between Swedish universities has been emphasized by some academic respondents to the questionnaire. This could be the tool to obtain a state of critical mass and avoid the draining of competence to USA and Asia.

Vision for 2030 and Beyond

By 2030, 2D materials have created a positive impact on Sweden through contributions to products, industry, society, and sustainability goals. 2D materials are a Swedish industrial area of strength, where materials and products make a clear contribution to Swedish industry's international competitiveness. The Swedish ecosystem for 2D materials is competent, complete, and stable [62].

The Global Challenges

The use of 2D materials contributes to achieving the UN global goals for sustainable development. In this case, specific attention is given to goal no 3, *Ensure healthy lives and promote well-being for all at all ages*. In particular, the following subgoals are addressed:

- Access to safe, effective, quality, and affordable essential medicines and vaccines for all (3.8)
- Early warning, risk reduction and management of national and global health risks, including reducing bloodstream infections due to selected antimicrobial-resistant organisms (3d)

The Materials
For biotechnological and medtech applications, Swedish industry have access to (certified) 2D materials with high and consistent quality. Standards for both 2D material's physicochemical properties, as well as their safety aspects are available. The health and safety issues of 2D materials are largely clarified. The understanding of how 2D materials affect mammalian and bacterial cells as well as viruses has improved, both regarding 2D material functionalized surfaces and in formulations. The actual *in vivo* antimicrobial performance and biocompatibility is well understood.

The Market Value Chain
The unique added values of 2D materials in biotech/medtech/life science applications are clearly defined. Functional value-chains from research to market exist. Large biotechnology companies will be involved in the development of new products together with start-ups, academia, research institutes and health care organizations.

The Eco-system
The important networking and support opportunities for Swedish 2D material community continues. There will be impact-oriented and earmarked financing for 2D materials in biotechnology application after Graphene Flagship and SIO Grafen ends.

International Collaboration
The Swedish actors are highly engaged on the European scene both in terms of research and development, value chains and product sales.

Conclusions and Recommendations

It is imperative that biotech and life science companies gain knowledge and confidence in 2D materials capabilities and their supply. Furthermore, the 2D material suppliers are still small and need financial security as well as help to **evaluate the USP** of their materials in biotech applications. Both needs to be developed alongside each other unless undue long timeframes would be the result.

It is clear that **creating a strong cross-disciplinary eco system and supporting complete value chains in Sweden** is of utmost importance for this area, since the abovementioned applications will still be at a low TRL even in 2030. However, the current eco-system which needs help expanding into the biotech area may be left without targeted support. There is therefore a clear danger that the potential of 2D materials in biotech will not land in Swedish innovations.

We recommend **dedicated public funding for collaboration within a platform dedicated to advanced materials and their biotech applications**. The platform should be a center organizing collaborative projects, workshops, information dissemination etc. The platform needs to work in an international context regarding research and innovation. A biotech center should be the lead, and the existing networks, including SIO Grafen, should be part of such a development.

The platform should strengthen collaboration between the established tech companies, start-ups and the material producers together with healthcare professionals, academia and research institutes.

The focus areas could be (i) developing the right key performance indicators of the materials and products to **cut down access time to the market** (ii) **health and safety characterization**, (iii) **mechanistic understanding** of the interactions of 2D functionalized materials with biological systems and (iv) **work performed in standardization committees.**

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