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DELIVERABLE 1.1

HUMAN RECEPTORS MAP

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PROJECT CO-ORDINATOR: UDC
Coordinator's Organization Name: Universidade da Coruña

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WP4 Test and validation of the final device

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PU	Public	X

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Responsible Author	Tea Carletti			
Contributions from	Kirti Shila Sonkar, Alessandro Marcello, Ivan Coluzza.			

Background on FLUFET

Infectious zoonotic diseases that jump from animals to humans are on the rise, and the risk of a new pandemic is higher now than ever before. Future health models need to consider the close connection between human and animal health, and new technologies capable of continuously monitor places where the risk of pathogens transmission is higher (shared by animals and humans) are urgently needed to prevent the human, socio-political and economic cost from pandemics.

Continuous monitoring and harmonized data collection of animal farms are required by the European Parliament. However, current methods are not suitable for an in-situ, continuous and automatic detection, so today only a limited number of specific pathogens are monitored.

FLUFET will be the first automatized sensor able of continuously detecting a broad spectrum of viral targets, and with the unprecedent capability of detecting unknown viruses. This sensor will be based on graphene Field Effect Transistors (gFETs). FLUFET will detect infectious zoonotic threats before they spread to humans and create potential outbreaks, opening the door for a pandemic's prevention continuum. It will bring the possibility to incorporate the long-distance external factors heavily affecting human health at worldwide level.

FLUFET brings interesting opportunities for Health and pandemics experts and managers, Policymakers and regulatory/ standardization bodies, Animal farmers and their associations, Precision livestock farming solution providers, Investors and researchers in the multiple disciplines involved in the consortium.

FLUFET requires an interdisciplinary consortium including partners from computational biophysics, graphene technology, nanotechnology, sensing, microfluidics, virology, surface engineering and sensor design and electronics

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Consortium Members

Nº	Role	Short Name	Legal Name	Country	PIC
1	COO	UDC	Universidade da Coruña	ES	999629718
2	BEN	BCMaterials	FUNDACION BCMATERIALS - BASQUE CENTRE FOR MATERIALS, APPLICATIONS AND NANOSTRUCTURES	ES	928273511
3	BEN (IO)	INL	Laboratorio Iberico Internacional de Nanotecnología	PT	988145985
4	BEN	BIOMA	ASOCIACION CENTRO DE INVESTIGACION COOPERATIVA EN BIOMATERIALES- CIC biomaGUNE	ES	998347572
5	BEN (IO)	ICGEB	INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY	IT	999470444
6	BEN	GSEMI	GRAPHENEA SEMICONDUCTOR SL	ES	910983940
7	BEN	VTT	TEKNOLOGIAN TUTKIMUSKESKUS VTT OY	FI	932760440

History of Changes

Version	Issue Date	Stage	Description	Comments	Contributor
1.0	26.08.2024	Draft	First Draft of D1.1		Tea Carletti Kirti Shila Sonkar
1.1	27.08.2024	Draft	Internal Review		Alessandro Marcello
1.2	27.08.2024	Final	Final version		Tea Carletti

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D1.1 – HUMAN RECEPTOR MAP. Map of the relationship between known viruses and their target human receptors.

1.1. INTRODUCTION

Viral infections pose a significant threat to global health, with frequent outbreaks and pandemics (Abbey et al., 2020). Pandemics caused by infectious zoonotic diseases, i.e. infectious disease caused by a pathogen that can jump from a non-human to a human host, are of concern. Factors such as deforestation and agricultural expansion increase the risk of zoonotic disease spillover by bringing humans and animals closer together. In the past few years numerous disease outbreaks have had suspected or confirmed zoonotic origin (e.g. Mpox, Ebola virus and COVID-19). Rapid and accurate detection of viral infections is crucial for effective disease management and prevention. The efforts at international levels to be prepared for another possible pandemic is huge. WHO, back in 2015, created the WHO Research and Development (R&D) Blueprint, a global strategy and preparedness plan to accelerate the development of medical countermeasures when facing a new epidemic/pandemic. The WHO R&D Blueprint recently published the document "Pathogen Prioritization – A scientific framework for epidemic and pandemic research preparedness" (WHO-R&DBlueprint, June 2024), which rank a list of prioritized pathogens family, including *Disease X*, a term used to describe a currently unknown pathogen with pandemic potential (WHO, 2018). To complement this efforts, several other institutions are developing disease rankings at national and global levels, including the U.S. Centers for Disease Control and Prevention (CDC) who created the Priority Zoonotic Diseases Lists, facilitated by the U.S. Centers for Disease Control and Prevention, and the Coalition for Epidemic Preparedness Innovations (CEPI) who has partnered with the University of California, Davis, to expand SpillOver, a platform that assess the pandemic potential of various viruses by considering environmental, host, and viral risk factors (Jane Fieldhouse, 2024; Kerlin, 2021). Additionally, the ZOVER database integrates data from bat- and rodent-associated viruses (DBatVir and DRodVir) and includes up-to-date knowledge on mosquito- and tick-associated viruses, aiding in the surveillance and prediction of emerging infectious diseases (Zhou et al., 2022).

1.1.1. VIRUS RECEPTORS AND BIOSENSORS

Biosensors offer a promising approach to achieving rapid and accurate detection of viral infections, and virus receptors are key targets for their development (Wan et al., 2020; Kim et al., 2023). Virus receptors are molecules on the surface of host cells recognized by viruses, facilitating entry and infection. For this purpose, viruses can also use co-receptors, accessory proteins, and different attachment factors, increasing the complexity of the relationship between virus-receptors. These receptors can be proteins, carbohydrates, or lipids, and their specificity and affinity for viral particles make them ideal targets for biosensor development (Maginnis, 2018).

1.1.2. CLASSIFICATION OF VIRUS RECEPTORS

Cellular receptors exploited by mammalian viruses can be classified into three main types based on their structure and function:

- **Glycoconjugates**: Including glycoproteins (e.g., sialic acid receptors for influenza virus) and glycolipids (e.g., Histo-blood group antigens (HBGA) on type 1, 2, and 3

GSLs for Human Norovirus (HuNoV), that serve as attachment sites for viral particles (Ayora-Talavera, 2018).

- **Proteinaceous receptors**: such as CD4 for HIV, which directly interact with viral particles (Matthias et al., 2010).
- **Polysaccharide receptors**: comprising carbohydrate molecules (e.g., heparan sulfate for HSV) that bind to viral particles (Itakura et al., 2020).

1.2. THE FLUFET PROJECT

The FLUFET project aims to create an automated sensing device capable of continuously detecting a broad spectrum of viral targets. To achieve this, a graphene field-effect transistor will be functionalized with human receptors that will recognize and bind viruses, sending an alarm to the system. Therefore, it is crucial to maintain an updated map of human receptors and their interactions with viruses. As shown in Figure 1, the number of articles describing novel virus-receptor interactions has been increasing since 2000, with approximately 29 new interactions described per year. Considering the constant increase in knowledge in this field, we set ourselves the goal of keeping this map up to date in the coming years and trying to assign a score based on the risk to human health.

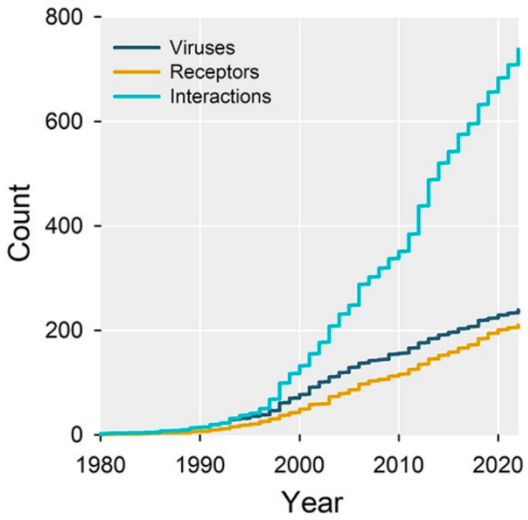

Figure 1 – Annual discovery rates of distinct virus-receptor interactions, viruses, and host factors. Adapted from (Valero-Rello et al., 2024).

1.3. SYSTEMATIC ANALYSIS OF VIRUS RECEPTORS

To build our map, we used the systematic analysis by Valero-Rello and colleagues (Valero-Rello et al., 2024), which considers all host factors promoting viral entry through direct interactions with viral particles. This includes:

- **Main receptors**: necessary and sufficient for viral entry.
- **Alternative receptors**: sufficient but not necessary for viral entry.
- **Co-receptors**: necessary but not sufficient.
- **Accessory receptors**: promoting entry but not necessary or sufficient.
- **Attachment factors**: moieties that promote initial virus binding.

The authors performed initial research on PubMed of mammalian virus names associated with keywords such as “receptor”, “attachment” and “binding”. The research gave 67492 results which were filtered through text mining and manual revision. Combining this initial research

with available databases (ViralZone, KEGG, VTHunter) and meta-analyses (Zhang et al., 2019; Wang et al., 2020; Chen et al., 2022), they obtained a final dataset of 210 cellular factors, 239 viral species, and 738 total interactions.

The table below summarizes the results they obtained classified according to the nature and role of the host factors involved.

Nature	Role	Total (Percentage)
Proteins	Main receptor	164 (22.2%)
	Alternative receptor	166 (22.5%)
	Co-receptor	79 (10.7%)
	Accessory receptor	207 (28.0%)
Moieties	Attachment	122 (16.5%)
Total		**738 (100%)**

Table 1 – Virus-receptor interactions classified according to the nature and role of the host factors involved. (Table from Valero-Rello, Baeza-Delgado et al. 2024)

Interestingly, among the 738 virus-host interactions identified, 616 involved protein receptors, while 122 interactions were regulated by attachment molecules. Most of these moieties were sialic acids or other glycans such as heparan sulfate. Knowing the abundance on the cellular surface of such molecules, bound to proteins or lipids, this data suggests that there might be a significant number of yet unknown interactions between viruses and humans which are regulated by these surface molecules.

1.3.1. BROAD-SPECTRUM VIRUS DETECTION

From the 738 total interactions identified by Valero-Rello and colleagues it's evident how some receptors are used by many viruses. Examples include CD209, also known as DC-SIGN, which recognizes a variety of viruses from 13 different viral families and sialic acid, a sugar that can be found bound to proteins or surface lipids, which is used as an attachment molecules by several strains of influenza viruses as well as by other virus such as MERS or SARS-CoV-2. Considering the plasticity of some of these receptors we can speculate that these molecules could be useful targets for broad-spectrum viral detection because of their capacity to bind to multiple viruses.

1.4. MAP OF HUMAN RECEPTORS-VIRUS INTERACTION

The map we created consists of a list of all known virus-human receptors interactions, adapted from the work of Valero-Rello and colleagues.

The map is attached to this report as *Annex 1_Virus-Receptors Map and Ranking.*

In the table that we created it is indicated: name of the virus, viral family, name of the receptors or family of receptor for which it has been proved an interaction with a specific virus, nature of the receptors (lipid, protein or sugar), role of the receptor in the interaction (main receptor, alternative receptor, co-receptor, accessory or attachment, as described in paragraph1.3), name of the gene encoding the protein receptor and, finally, two different ranking systems of how risky the viruses listed in the map are for humans.

The first one, named “SpillOver Score” consist in the value assigned for that specific virus by the platform SpillOver, described in introduction, which calculate the *risk score* of a virus taking in consideration several factors such as: host plasticity, if animal-to-human and human-to-human transmission has been proved for that virus, geography distribution of the host and other animals found infected, frequency of interaction between animals and humans in the host ecosystem, land use in host ecosystem, livestock and human population density in the host ecosystem, if the virus has already caused an epidemic or a pandemic and many other risk factors. We highlighted the risk score with a color scale where red correspond to the most dangerous virus and orange to the less dangerous. In grey are the viruses which are not reported in the SpillOver database. This ranking system consider the only zoonotic viruses.

The second ranking system we used is the one suggested by WHO in the most recent report of the R&D Blueprint “Pathogen Prioritization”. In this report they clearly indicate which family of viruses and pathogens are priority for WHO and so need to be investigated as well as diagnostic methods need to be developed in order to be prepared in case one of these pathogens may cause an epidemic or a pandemic. The approach of supporting research in the entire family, instead of focusing on a specific pathogen, helps mitigate the risk of missing potential pandemic pathogen. Here they rank the “Public Health Emergencies of International Concern (PHEICs) Risk” as High, Medium, Low-Medium and Low which we report in our table as color coded: Red, Orange, Light-Orange and Yellow respectively. In grey the viral families which are not listed as priority in the WHO report.

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