GSK in Italy and worldwide: focus on vaccines

Davide
Head of Preclinical R&D (Vaccines)
Siena, Italy
Who we are

A science-led global healthcare company with a special purpose: to help people do more, feel better, live longer.

We have 3 global businesses and 95,490 employees worldwide which research, develop and manufacture innovative pharmaceutical medicines, vaccines and consumer healthcare products.
Our Pharmaceuticals business has a broad portfolio of innovative and established medicines with commercial leadership in respiratory and HIV.

We are strengthening our pipeline through a focus on immunology, human genetics and advanced technologies to help us identify the most promising new medicines.

2.3bn packs of medicines sold in 2018

£17.3bn 
Sales turnover 2018

Immune system T-cells attacking a cancer cell
Founded in 2009, it is a joint venture that combines the competences of GSK (78.3%), Pfizer (11.7%) and, since 2012, Shionogi (10%).

With **12 treatments in portfolio and 6 in pipelines**, ViiV Healthcare is committed to providing and continuing to develop new treatment options for people living with HIV / AIDS.
Vaccines

We are the leading Vaccines company in the world, thanks to a broad portfolio and an innovative pipeline helping protect individuals throughout their lives.

In 2018 we delivered **770 millions doses** of vaccines in **158 countries**, over **2 million doses every day**.

- 3 research centers in USA, Italy, Belgium
- **13** manufacturing sites
- **25** vaccines available in Italy

**£5.9bn**
Sales turnover 2018

Herpes zoster virus of shingles
Our Consumer Healthcare business develops and markets an innovative portfolio of consumer preferred and expert recommended brands in the Oral health, Pain relief, Respiratory, Skin health, Nutrition and Digestive health categories.

In 2018 3,8 bn consumer healthcare products delivered worldwide.

£7.6bn
Sales turnover 2018

Novamin, a key technology in Sensodyne Repair and Protect
GSK in Italy: where we are

Verona
- GSK – offices
- ViiV - offices

Baranzate
- GSK Consumer Healthcare - offices

Parma
- GSK Manufacturing – manufacturing site

Siena e Rosia
- GSK Vaccines – R&D center
- GSK Vaccines – manufacturing site
- GSK Vaccines - offices
- GSK Vaccines Institute for Global Health – research center
GSK Vaccines in Italy
GSK Vaccines
Two forefront sites in Tuscany, an important player nationwide

Rosia
Manufacturing site

Siena
Global R&D center

356 million* euros
GSK Vaccines srl turnover 2018
(direct sales + export and services)

* Provisional data pending the final adoption of the budget

About 190 million spent
in 2018 for products and services

- 68% spent in Italy
- 32% spent in the rest of the world
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1904</td>
<td>Achille Sclavo founds in Siena the Istituto Vaccinogeno e Sieroterapico Toscano Sclavo</td>
</tr>
<tr>
<td>1970</td>
<td>Inauguration of the Research Center in Siena</td>
</tr>
<tr>
<td>1997</td>
<td>First adjuvanted flu vaccine</td>
</tr>
<tr>
<td></td>
<td>Reverse vaccinology: a revolutionary approach to develop MenB vaccine</td>
</tr>
<tr>
<td></td>
<td>Craig Venter sequences the genoma and collaborated with Rino Rappuoli to develop the new technique</td>
</tr>
<tr>
<td>2010</td>
<td>Men ACWY vaccine against four serotypes of meningococcus</td>
</tr>
<tr>
<td>2015</td>
<td>FDA approval of MenB vaccine</td>
</tr>
<tr>
<td></td>
<td>First MenB mass vaccination campaign in UK</td>
</tr>
<tr>
<td>1963</td>
<td>Albert Sabin selects the Sclavo institute for the manufacturing of its Polio vaccine</td>
</tr>
<tr>
<td>1972</td>
<td>Operations start in Rosia</td>
</tr>
<tr>
<td>2001</td>
<td>Men C vaccine</td>
</tr>
<tr>
<td></td>
<td>First approval in Europe of the vaccine against meningococcus C</td>
</tr>
<tr>
<td>2013</td>
<td>Men B vaccine EMA approval</td>
</tr>
<tr>
<td>2018</td>
<td>Over 22 million doses of MenB distributed worldwide</td>
</tr>
</tbody>
</table>
Preclinical Identification antigens (molecules that stimulate a protective immune response)

Explorative step Medical need, epidemiology, feasibility

Release The vaccine can leave, to reach our customers

Packaging The vaccine is labelled and packed

Formulation filling and inspections In order to ensure the highest quality of vaccines

Bulk manufacturing Bacteria are grown and transferred to fermenter, then inactivated and vaccine components are purified

Clinical Development Evaluation of the safety, efficacy and medical benefit of the candidate vaccine

Technical Research Transforming antigens into robust vaccine products

Registration Dossier development, submission and approval

GSK Vaccines Italy
Siena e Rosia cover all phases of Life-cycle of the vaccine
We contribute to the **GSK Vaccines strategy**, driving vaccine R&D projects through innovation, cutting edge science, talented people and strategic collaborations with scientific communities and the leading national and international research bodies.

**People**

More than **500 employees**

**Investments**

About **€ 370 million** investments in R&D managed by Siena between 2015 and 2018

**Cutting-edge Technologies**

We develop many of the most innovative vaccines currently available
Siena: Research and Development

Our R&D Centre milestones

We were the **first in the world** to reach the following **achievements**:

- **1993**: Vaccine against **pertussis**
- **1997**: **Reverse vaccinology** development
- **1997**: The first flu vaccine with **MF59 adjuvant**
- **2004**: Meningitis B eradicated in New Zealand
- **2000**: Meningitis C eradicated in UK
- **2010**: MenACWY the first tetravalent pediatric vaccine
- **2013**: Vaccine against Meningococcus B
Rosia: Manufacturing and Quality Control
Center of excellence for the production of glyco-conjugate vaccines

Relevant figures
More than 47 million doses packed in 2018, distributed in 54 countries
About 1,500 employees

Investments
€ 167 million invested in infrastructures and manufacturing plant 2015/2018

Attention to Quality
+70% of production time of a vaccine is absorbed by quality controls
Vaccines produced in Siena and Rosia
The only site to produce the two GSK blockbuster: MenB and herpes zoster

Meningitis
- Meningococcus A, C, Y, W-135
- Meningococcus C
- Meningococcus B

Travelling*
- Rabies
- Tick-borne Encephalitis
- Tetanus

Herpes zoster*
*Secondary Ops only
The future of vaccinology pass through here
An integrated scientific ecosystem
Attracting talents, investments and valuable partnership

Sclavo Vaccine Association
Master in Vaccinology
Sciences Academy
International School
University of Siena
GSK Vaccines Institute for Global Health (GVGH)
Toscana Life Sciences Foundation
Classical approaches to vaccine development

Isolate -> Inactivate -> Inject

Limitations:

- Technical and safety problems associated with large scale pathogen production
- Vaccine discovery can be time consuming and inefficient (multiple rounds of purification-testing)
- Difficult to tackle microbial diversity
Reverse Vaccinology 2.0: Human immunology instructs vaccine antigen design

**CLASSICAL VACCINOLOGY**
growing pathogens

- virus
- bacterium
- parasite

**REVERSE VACCINOLOGY**
design from information

- genome
- proteome
- structure
- mAb
- B cell

**vaccine**

Rappuoli, Bottomley, D’Oro, Finco, De Gregorio JEM April 2016
Neisseria meningitidis

- Encapsulated, aerobic, Gram- diplococcus
- Major cause of septicemia and meningitis after introduction of Hib and PCV7
  - Strictly human pathogen
  - Asymptomatic carriage is common
    - Carrier prevalence: ~1%–35%
  - Transmission
    - Respiratory secretions/ direct contact
    - Incubation period: 2–10 days
- >95% of total cases of invasive disease are caused by 5 major serogroups: A, B, C, Y and W135 (X is emerging)
The distribution of serogroups varies globally.

Epidemic and endemic disease are caused primarily by 5 serogroups: A, B, C, W-135, and Y.

Adapted from Harrison et al, Vaccine 2009
Reverse Vaccinology and Men B Vaccine Development

Complete *N. meningitidis* genome sequence

Bioinformatic analysis

Protein expression in *E. coli*

Protein purification and immunization

Final candidates selected for vaccine development

Confirmation of surface exposure

Confirmation of bactericidal activity

Vaccine

Genome-based approaches have been used to target other pathogens.

- **Group B Streptococcus**
- **Group A Streptococcus**
- **Pneumococcus**
- **Chlamydia trachomatis and Pneumoniae**
- **Tuberculosis**
- **Meningococcus**
- **Malaria**
- **Porphyromonas gingivalis**
- **Yersinia pestis**

**Antibiotic resistant!!!!**
- Staphylococcus
- C. difficile
- Pseudomonas

**Surface antigens not abundant**
**Immune evasion strategies**
**Antigenic sequence variation across strains**
**Low stability of antigens when expressed as recombinant proteins**
Functional insights into pathogen biology from integrated structure-based approach.

Similar protein structure share similar biological function.

Semantic search (180 external DBs)

GEMINI: 3D Protein similarity searching tool

3D GSK protein structures repository

Protein of unknown function

Structure, abundance and localization of surface-exposed proteins by "cryo-tomo, cryo-EM, X-ray"*

New Vaccine candidates

*In GSK Siena and GSK Pharma, UK
School, university, training: investing in the future
Sciences Academy
Center of excellence for future vaccine leaders

Founded in 2008 with the ambition to train the best talents in the field of vaccines research and development, in collaboration with universities.

The Sciences Academy has pioneered a number of innovative educational programs in vaccinology including PhD and Post-doctoral programs, helping over 300 students/fellows to graduate.

The program offers a unique opportunity for young researchers from all over Europe to be part of a world-class scientific environment supported by scientists and experts.
GSK meets the school

The objective of this initiative is to contribute to disclose the importance of the scientific culture among the local young people, starting from the daily work behind the production of a vaccine.

Every year the project sees the collaboration of various professionals figures from Siena and Rosia working in Research, Development, Manufacturing and Quality through a series of meetings within classroom and in the company.

The interactive story of a vaccine's life cycle becomes an occasion to share the human and professional paths linked to the great challenges of scientific research and innovation.
ITS Vita Foundation

We are among the **founding members of the VITA Foundation**: an high technological specialized school for the preparation of young people in **life sciences**.

GSK collaborates in a two-year **Probits course** for **young people between 18 and 30**, which trains senior Technicians for research and development of biotechnological products and processes.

In the period 2018/2019, **45 GSK employees have been involved** as teacher for classroom and labs sessions, with a total of **186 hours of lessons**. More than **20 internship opportunities** within the company.
GSK Vaccines Institute for Global Health
There is still a high global burden of infectious diseases

Global, all age deaths

Deaths per year

Almost all deaths are in low and middle income countries.

92% of deaths from infectious disease are in LMIC.

Global, all age deaths

Deaths per year

- High Income Countries
- Low & Middle Income Countries

Almost all deaths are in low and middle income countries

Global Deaths from Infectious diseases – GBD2015 data

Global, all age deaths

47% of deaths are from diseases for which there is NO registered vaccine

Vaccines are a highly effective public health measures

Huge burden of disease remains in developing countries for infectious diseases for which

- Vaccines do not exist but **could be developed**
- Vaccines exist, but are **not affordable** or do not match local needs

Need to develop safe, effective and affordable vaccines
GSK Vaccines Institute for Global Health (GVGH)

Our vision
Develop effective and affordable vaccines for neglected infectious diseases of impoverished communities
Translate laboratory concepts into high quality vaccines reducing the risk for commercial manufacturers

Vaccine conception

Vaccine growth and maturity

Vaccine gestation and incubation
Located in Siena, Italy, on the same campus as GSK Vaccines

100% owned by GSK but is a separate legal entity from GSK Vaccines

Project selection focused on public health needs for neglected diseases of impoverished communities

“Neglected” – not in development by major vaccine company

About 50 people in Technology platform, Technology Development, and Clinical Development & Regulatory Affairs

Actively seeks partners to fund research and development activities, particularly for production and clinical trials
Projects and platforms

- **In House Vaccine projects**
  - Multivalent *Shigella*, including *S. sonnei* component as concept
  - Invasive nontyphoidal *Salmonella*
  - Group A Streptococcus

- **Collaborative vaccine projects**
  (Licensed to Biological E)
  - Conjugate vaccine for *S. Typhi*
  - Bivalent conjugate vaccine for *S. Typhi* + *S. Paratyphi A*

- **Platform technologies**
  - GMMA – generalized modules for membrane antigens

The 4 GVGH target diseases cause 1 million deaths per year: 20% of the deaths from diseases for which there are no registered vaccines.
GMMA: A story about appropriate vaccine technology

USA Navy Typhoid Admissions

Admissions per year per 100,000 sailors

Year

1890 1900 1910 1920 1930
The 1913 typhoid vaccine

- Very Effective
  - Numerous field trials and human challenge experiments
  - Long lasting protection - > 20 years
  - Saved numerous lives

- Very Affordable
  - Low technology production
  - “Whole cell” vaccine – killed bacteria
  - Still commonly used technology for veterinary vaccines

- Significant Side Effects
  - Sores at the injection site
  - High fever and flu like symptoms
A vaccine with the efficacy and affordability of whole cells

But without the side effects

- Protective antigens are in the outermost layer but only a tiny part of whole cell vaccine is the “outer layer”
- Solution – we just want the outside layer!
Tricking bacteria into shedding the outer layer

*Effective & affordable vaccines without the side effects of whole cell vaccines*

- GMMA are released yielding pure source of outer membrane
  - Similar size to virus-like particles
  - Contain PAMPs: naturally adjuvanting
  - Multiple antigens are presented in their natural environment and conformation

- Genetic modifications trick bacteria into shedding outer membranes
GMMA-based vaccine manufacturing process

Generic, industrially scalable and economic process

Fermentation → Microfiltration → Ultrafiltration → Sterile filtration → Formulation

- Fermentation
- Microfiltration
- Ultrafiltration
- Sterile filtration
- Formulation

**GENERIC:** Already applied to several pathogens

**INDUSTRIALLY SCALABLE:** 8 GMP lots Drug Substance (DS) and 2 GMP Drug Product (DP) manufactured

**ECONOMIC:**
- From 30 L ferm, >150000 doses (S. sonnei)

## Methods for GMMA characterization

<table>
<thead>
<tr>
<th>Aim</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size and aggregation status</td>
<td>SEC-MALS/dls/TEM/NTA</td>
</tr>
<tr>
<td>Total protein quantification</td>
<td>Lowry assay, micro BCA</td>
</tr>
<tr>
<td>OAg identity and quantification</td>
<td>HPAEC-PAD, competitive ELISA</td>
</tr>
<tr>
<td>Purity (e.g. from soluble proteins, DNA)</td>
<td>HPLC-SEC</td>
</tr>
</tbody>
</table>


### On key surface molecules

<table>
<thead>
<tr>
<th>Aim</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAg identity</td>
<td>1H NMR, immunological assay, HPAEC-PAD</td>
</tr>
<tr>
<td>OAg molecular size distribution</td>
<td>HPLC-SEC</td>
</tr>
<tr>
<td>OAg OAc content</td>
<td>1H NMR, colorimetric</td>
</tr>
<tr>
<td>Lipid A structure</td>
<td>MALDI-MS</td>
</tr>
<tr>
<td>Lipid A content</td>
<td>HPLC-RP QQQ, HPLC-SEC/semicarbazide</td>
</tr>
<tr>
<td>Protein antigens identification/quantification</td>
<td>WB, RP-HPLC, capillary electrophoresis, SRM, competitive ELISA</td>
</tr>
</tbody>
</table>
GMMA are well tolerated and immunogenic in adult population

Launay et al. EBioMedicine 2017;22:164;
- Vega Masignani: vega.x.masignani@gsk.com
- Ilaria Ferlenghi: ilaria.x.ferlenghi@gsk.com
- Francesca Micoli: francesca.x.micoli@gsk.com