Vaccine Development for Sexually Transmitted Infections

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Outline

- STI vaccine roadmap
- Herpes simplex virus (HSV) vaccine development update
- *Chlamydia trachomatis* vaccine development
STIs and Global Public Health

- STIs have a profound impact on sexual, reproductive, and maternal-child health.
- STI control essential for achieving goals of global health agenda.
- New Global Health Sector Strategy for STIs endorsed at WHA.
  - STI vaccine development noted as key step for future STI control.
More than 1 million STIs acquired every day

- Estimated 377 million incident infections with chlamydia, gonorrhea, syphilis, trichomoniasis, HSV-2 in 2012

Effectively addressing STIs can have the following benefits:

- Improving neonatal outcomes
- Preventing cancer
- Decreasing burden of infertility
- Reducing HIV transmission
- Combating antimicrobial resistance
- Supporting health of young people

Source: IPPF
Current Control Challenges

- Limits to progress made with condom promotion as main prevention measure
- Most infections asymptomatic and lack of feasible tests in many settings
- Antimicrobial resistance: drug-resistant gonorrhea
- Stigmatizing, little public policy attention: without simple intervention, harder to garner support
WHO and NIAID Technical Consultation on STI Vaccines and Special Issue of Vaccine

- Need, development status, and future prospects for STI vaccines
  - Herpes simplex virus (HSV)
  - Chlamydia trachomatis
  - Neisseria gonorrhoeae
  - Trichomonas vaginalis
  - Treponema pallidum (syphilis)

- Global roadmap to move forward

Available at: http://www.sciencedirect.com/science/journal/0264410X/32/14
## STI Vaccine Roadmap: Nine Priority Action Areas

| 1. Obtain better epidemiologic data | 6. Define preferred product characteristics for 1st generation vaccines |
| 2. Improve understanding of STI natural history, burden of sequelae | 7. Expedite clinical development and evaluation |
| 3. Model the theoretical impact of STI vaccines | 8. Plan for vaccine introduction in advance |
| 4. Advance basic science research for STI vaccines | 9. Encourage investment in STI vaccine development |
| 5. Conduct basic & translational studies in human clinical settings as soon as possible | |

World Health Organization

National Institute of Allergy and Infectious Diseases
Update to Roadmap

The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps

Sami L. Gottlieb, Carolyn D. Deal, Birgitte Giersing, Helen Rees, Gail Bolan, Christine Johnston, Peter Timms, Scott D. Gray-Owen, Ann E. Jerse, Caroline E. Cameron, Vasee S. Moorthy, James Kiarie, Nathalie Broutet
Current Status of the Development Pathway of STI Vaccines

- Basic research: Trichomonas vaginalis
- Preclinical development: Neisseria gonorrhoeae, Treponema pallidum
- Clinical evaluation: Chlamydia trachomatis, Herpes simplex virus

World Health Organization
National Institute of Allergy and Infectious Diseases
Outline

- STI vaccine roadmap
- Herpes simplex virus (HSV) vaccine development update
  - Epidemiology and roadmap activities
  - HSV vaccine pipeline and early clinical trials
  - Next steps
- Chlamydia trachomatis vaccine development
Impact of Genital Herpes: The Case for a Vaccine

- Leading cause of genital ulcer disease worldwide
- Impact on quality of life
- HIV-1 acquisition and transmission
- Neonatal herpes
HSV-2 estimates: 417 million infections globally in 2012

Finalized estimates of HSV-1 infection

Better data on neonatal herpes
  - Global estimates
  - CHAMPS evaluation

HSV vaccine business case
  - Modelling
  - HSV-HIV interaction
Large Global Burden of HSV-1 Infection, Increasing Role of Genital HSV-1

- Estimated 3.7 billion people (67%) aged 0-49 with HSV-1 infection globally

- 140-239 million adults with genital HSV-1 infection
  - Genital HSV-1 primarily in HICs
  - In Africa and SE Asia, most have HSV-1 by sexual debut

- Taken together with HSV-2, more than half a billion people with genital HSV infection worldwide

Public Interest in HSV-1 Estimates

Two-Thirds of the World Has Herpes, Health Group Says

That's more than 3.7 billion people.

Two-thirds of the globe's population has herpes, according to the World Health Organization.

That's more than 3.7 billion people under the age of 50. Nearly 60% of the population, the organization said Friday. There are two types of the herpes simplex virus, an infectious and incurable condition. HSV-1 is primarily transmitted through oral contact and causes cold sores around the mouth, while HSV-2 is sexually transmitted and causes genital herpes.

More than half the world has herpes, WHO reports huff.to/1NB7jGH

World Health Organization to planet: We're pretty sure most of you have the herpes virus

Fresh off its buzzkilling revelation earlier this week that you might get cancer from bacon and burgers, the World Health Organization is back with a...
Preliminary WHO Global Neonatal Herpes Estimates

- Applied HSV-1/2 prevalence/incidence to birth rates, then applied published risks of mother-to-child transmission

- Estimated new cases globally
  - 60% fatality rate without treatment
  - Long-term neurologic deficits common even with therapy

- Estimates submitted for publication

Looker K et al, manuscript under review, 2016
Neonatal Herpes Implications

- Several reasons to believe true numbers may be higher than estimated for LMICs
  - Fewer Caesarean sections
  - Greater HIV prevalence: increased HSV shedding at delivery
- Less infrastructure: neonatal herpes may be missed, higher burden of death
- Need for primary data in LMICs: CADMIA & CHAMPS
  - Preliminary CADMIA validation data: Of 41 neonatal deaths evaluated, 2 cases of neonatal HSV as final cause of death
  - Ongoing evaluation in further CADMIA validation and new CHAMPS Network will incorporate HSV-1 & HSV-2 testing

Preliminary data from CADMIA pilot study courtesy of C. Menendez, Barcelona Institute for Global Health/WHO
HSV Vaccine Business Case

- Disease burden + costs
- Modeled vaccine impact
- Market demand
- PPCs / Target product profile
- Return on investment
- Vaccine development process + costs
- Basic science + technology
Better Epidemiologic Data and Modelling to Inform Business Case

- HSV-2 in GBD study 2013: >300,000 YLDs due to GUD
- STIMA: individual participant data meta-analysis, combined data from 18 prospective HIV prevention studies
- 2015 HSV vaccine modelling meeting
- Updated systematic review/meta-analysis of HSV-2 and HIV acquisition: analysis underway
- Review of biological mechanisms of HSV-HIV interaction and implications for vaccine development
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company</th>
<th>Candidate</th>
<th>Adjuvant</th>
<th>Current Phase</th>
<th>Results</th>
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<tbody>
<tr>
<td>Synthetic peptide complex with HHSP 70</td>
<td>Agenus</td>
<td>HerpV 32 peptides</td>
<td>QS-21</td>
<td>II, therapeutic</td>
<td>17% reduction in shedding, 75% reduction in viral load</td>
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<td>Recombinant subunit</td>
<td>Genocea</td>
<td>GEN-003 ICP4, gD2</td>
<td>Matrix-M2</td>
<td>II, therapeutic</td>
<td>60% reduction in lesion rate, 55% reduction in shedding</td>
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<td>DNA vaccine</td>
<td>Vical</td>
<td>VCL-HB01 gD, UL46/UL46</td>
<td>Vaxfectin</td>
<td>II, therapeutic</td>
<td>Pending</td>
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<tr>
<td>Replication defective HSV-2</td>
<td>Sanofi</td>
<td>HSV529</td>
<td>NA</td>
<td>I, prophylactic therapeutic</td>
<td>Pending</td>
</tr>
<tr>
<td>DNA vaccine</td>
<td>Amedus (Australia)</td>
<td>Amedus gD, codon optimized</td>
<td>Ubiquitin tagged</td>
<td>II, therapeutic</td>
<td>Interim data expected soon</td>
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</table>
Genocea’s GEN-003 Vaccine Shows Encouraging Results

March 31, 2016

Genital Herpes Immunotherapy GEN-003 Shows Sustained Reduction of Viral Shedding Rate, Durable Impact on Clinical Disease 12 Months Post-Dosing

- Consistent efficacy across potential Phase 3 clinical trial endpoints -
- Once-yearly or less frequent maintenance dosing expected -
- Company to host conference call at 9 a.m. ET today -

CAMBRIDGE, Mass., March 31, 2016 (GLOBE NEWSWIRE) -- Genocea Biosciences, Inc. (NASDAQ:GNCA), a biopharmaceutical company developing T cell-directed vaccines and immunotherapies, today announced positive 12 month efficacy data from its Phase 2 dose optimization trial evaluating GEN-003 for the treatment of genital herpes. GEN-003 demonstrated sustained and statistically significant reductions compared to baseline in the rate of viral shedding 12 months after dosing across multiple dose groups as well as sustained efficacy at multiple dose levels across secondary endpoints measuring the impact on clinical disease. GEN-003 was safe and well tolerated by patients, with no serious adverse events related to the vaccine in the trial.
GEN-003-002: Lesion Rates (% of days with lesions)

Slide courtesy of Seth Hetherington, Genocea Biosciences
NIH/NIAID HSV Vaccine Working Group

Started outlining desired characteristics for therapeutic and prophylactic vaccines:

- Indications and target populations
- Clinic trial design and endpoints
- Minimum efficacy and safety requirements

Summary and Recommendations from a National Institute of Allergy and Infectious Diseases (NIAID) Workshop on “Next Generation Herpes Simplex Virus Vaccines”

David M. Kniipe, Lawrence Corey, [...], and Carolyn D. Deal

Vaccine. Author manuscript; available in PMC 2016 Mar 10. Published in final edited form as: Vaccine. 2014 Mar 20; 32(14): 1561–1562. Published online 2014 Jan 28. doi: 10.1016/j.vaccine.2014.01.052
Next Steps: Opportunities for WHO Engagement

- Preferred product characteristics for HSV vaccines
- Consensus-building on clinical evaluation
  - Key endpoints for clinical trials
  - Steps needed to evaluate therapeutic vaccines in LMICs
- Partnering with countries and CHAMPS project to obtain better primary data on neonatal herpes in LMICs
- Coordination of HSV vaccine business case and modelling
  - Incorporating HIV, neonatal herpes, HSV-1
  - Considering therapeutic & prophylactic vaccines in LMICs
Outline

- STI vaccine roadmap
- Herpes simplex virus (HSV) vaccine development update
- *Chlamydia trachomatis* vaccine development
  - Unmet medical need
  - Current vaccine development efforts
  - Opportunities for WHO engagement
Chlamydia trachomatis

- Gram-negative obligate intracellular bacterium, can infect genital, ocular, and lung epithelium
- Serovars D-K: sexually transmitted genital infection and associated conditions
  - Serovars A, B, Ba, C: ocular trachoma
  - Serovars L1-L3: lymphogranuloma venereum
- Unique biphasic life cycle aids pathogen in avoiding host immune response
WHO estimates: 131 million new cases of chlamydia in 2012

Chlamydia disproportionately affects adolescents and young adults.

- Chlamydia prevalence can vary by population:
  - 7% in antenatal clinics in Africa
  - 25-30% in some Pacific Islands

BUT

- Consistently higher prevalence among adolescents, young adults

Chico et al, JAMA, 2012; WHO Regional Office of the Western Pacific, 2012
Upper Genital Tract Disease and Other Sequelae

- **C. trachomatis** can ascend to the upper genital tract and cause pelvic inflammatory disease (PID)

- Long-term sequelae
  - Tubal factor infertility
  - Ectopic pregnancy
  - Chronic pelvic pain

- Other complications
  - Preterm birth, neonatal conjunctivitis and pneumonia
  - Increased HIV risk
  - Epididymitis in men

Scanning electron microscopy photos courtesy of Dorothy L. Patton, University of Washington
Burden of Sequelae and Costs

- Global burden of chlamydia-associated PID, infertility and other sequelae not well characterized
- Estimates of infertility: 49 million to 186 million couples unable to have a child over 5 years
  - Number attributed to chlamydia unknown
- Global Burden of Disease Study 2013: 647,000 YLDs
- Global economic costs unknown, but in US, estimated $517 million annually
Chlamydia Natural History

- Estimated 68 million chlamydia infections among women annually
- If all left untreated, could mean close to 1 million new cases of infertility each year
Current Control Challenges

- Most infections asymptomatic and lack of feasible tests in many settings
  - LMICs: most chlamydia missed

- Screening programs difficult to bring to scale in HICs
  - Do not appear to have reduced chlamydia transmission

- Repeat infection rates 10-20% after treatment
  - Partner management challenging
Need for Chlamydial Vaccine in LMICs

- Might have most benefit in LMICs without adequate infrastructure for screening
- Likely highest burden of sequelae in LMICs
- Proportion of infertility that is tubal factor:
  - In US, 10-40% among women seeking fertility care
  - In sub-Saharan Africa, tubal factor in up to 65-85% of women
  - Most African data older; landmark study in 1980s

Cates et al, Lancet, 1985
Biologic Feasibility for Chlamydia Vaccine Development

- Large number of animal challenge studies showing at least short-lived natural immunity
- Human epidemiologic studies consistent
  - In cohort of 200 US women, those whose infections cleared spontaneously between testing and treatment were less likely to become re-infected on follow-up
- Trachoma vaccine trials in 1960s using whole killed organism preparations
  - Some protection against infection
  - Overall protection was short-lived and serovar-specific
Mechanisms of Immunity

- Well-established *C. muridarum* mouse model with vaginal infection and upper genital tract pathology
- Limitations but useful for understanding elements of immune response, consistent with available human data

Importance of:

- Tissue-resident IFN-γ producing CD4+ T cells
- Antibodies play some role

Image courtesy: Michael Starnbach, Harvard
Main Vaccine Approaches

- Subunit vaccines based on the chlamydial major outer membrane protein (MOMP)
- Whole inactivated vaccines
- Live attenuated (plasmid-deficient) vaccines

Enabled by scientific advances in:
- Genetic manipulation of chlamydia
- Reverse vaccinology and proteomics
- Novel adjuvants
## Chlamydia Vaccine Preclinical Pipeline

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company/Institution</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOMP VD4 neutralizing antibodies</td>
<td>Statens Serum Institut</td>
<td>Phase I trial expected to start in 2016</td>
</tr>
<tr>
<td>Intranasal nanoemulsion with MOMP</td>
<td>NanoBio Corporation</td>
<td>Preclinical (Beagley et al, unpublished)</td>
</tr>
<tr>
<td>MOMP + Pmps</td>
<td>Pan-Provincial Vaccine Enterprise Inc. (PREVENT) and BC-CDC</td>
<td>Preclinical</td>
</tr>
<tr>
<td>cSAP TLR7 agonist with UV-killed CT</td>
<td>Selecta Biosciences</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Vaxonella platform (salmonella vector)</td>
<td>Prokarium</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Live attenuated (plasmid-deficient) trachoma vaccine</td>
<td>NIH/NIAID</td>
<td>Phase I trial expected to start in 2017</td>
</tr>
</tbody>
</table>
NIH/NIAID Chlamydia Vaccine Workshop, May 2015

- Working groups to facilitate collaboration among academics, industry, government
- Standardized reagents, immunogens and assays
- Consensus on most appropriate animal models for vaccine evaluation
- Strategies to accelerate moving vaccine candidates into clinical evaluation
Critical Challenge: Clinical Endpoints

- Ultimate goal: Decrease upper genital tract sequelae, however challenges with PID as clinical endpoint
  - Clinical diagnosis insensitive, nonspecific
  - PID multi-factorial, typically *C. trachomatis* in 1/3 of cases
  - Clinical trial design considerations

- Accurate NAAT testing available for evaluation of infection
  - Disease outcomes may also be critical
  - Vaccine with only partial efficacy for infection at cervix may prevent ascension to upper genital tract
Opportunities for WHO Engagement

- Consensus building on clinical endpoints and trial design
- Research to identify better measures of tubal involvement and surrogate endpoints
  - Biomarkers, radiologic, other measures of upper tract ascension, infection, inflammation, damage
- Supporting collection of better data on global burden of disease sequelae and costs to make business case
  - Proportion of PID, infertility related to chlamydia, esp in LMICs
- Defining target population: adolescent vaccine for girls only versus girls and boys
- Advancement of joint WHO/NIAID STI vaccine roadmap and coordination of STI vaccine consortium
Thank you

- Nathalie Broutet
- Birgitte Giersing
- Christine Johnston
- Anna Wald
- Amanda Coleman
- Hagit David
- Toni Darville
- Tom Hiltke
- Taylor Poston