BIOTECHNOLOGICAL INNOVATION AND THE DEVELOPMENT OF BIO-BASED ECONOMIES

Session 2 - Innovation and intellectual property in the bio-economy age
Biotechnologies revolutionizing healthcare

Carlos M. Morel
Director
Center for Technological Development in Health (CDTS)
Oswaldo Cruz Foundation (Fiocruz)
The new science and the new biotechnology

Molecular biology, networks, barriers

The New Science and the New Biotechnology
Molecular biology: the basis of modern biotechnology

- 1938: the first occasion that the phrase ‘molecular biology’ appeared in print

The new science of Molecular Biology

- Key advances, 1938-1988
  - 1938: The term “molecular biology” is used for the first time (Warren Weaver, Rockefeller Foundation)
  - 1944: Transformation of Pneumococcus by DNA (Avery)
  - 1953: DNA as a double helix (Watson & Crick)
  - 1961: Theory of the operon (Jacob & Monod)
  - 1972: Recombinant DNA (Paul Berg)
  - 1975: Monoclonal antibodies (Kohler & Milstein)
  - 1977: DNA sequencing (Gilbert; Sanger)
  - 1985: Polymerase Chain Reaction (PCR; Kary Mullis)

Trends in Biotechnology 6:234-243

**Perspectives**

*Left* For centuries, creative individuals were embedded in an invisible college, that is, a community of scholars whose exchange of ideas represented the basis for scientific advances. Although intellectuals built on each other’s work and communicated with each other, they published alone. Most great ideas were attributed to a few influential thinkers: Galileo, Newton, Darwin, and Einstein. Thus, the traditional scientific enterprise is best described by many isolated nodes (blue circles). *(Middle)* In the 20th century, science became an increasingly collaborative enterprise, resulting in such iconic pairs as the physicist Crick and the biologist Watson (left), who were responsible for unraveling DNA’s structure. The joint publications documenting these collaborations shed light on the invisible college, replacing the hidden links with published coauthorships. *(Right)* Although it is unlikely that large collaborations—such as the D0 team in particle physics or the International Human Genome Sequencing Consortium pictured here—will come to dominate science, most fields need such collaborations. Indeed, the size of collaborative teams is increasing, turning the scientific enterprise into a densely interconnected network whose evolution is driven by simple universal laws.
The new industry of Biotechnology

• 1978: Genentech and Eli Lilly produce *insulin*
• 1980: Biogen produces *interferon*
• 1988: five proteins from genetically engineered cells approved as drugs by the Food and Drug Administration (FDA)
  – Synthetic insulin, human growth hormone, hepatitis B vaccine, alpha-interferon, tissue plasminogen activator
• End of 1990s’: > 125 genetically engineered drugs approved
From bench to bed: Crossing the Valley of Death

From bench to bed: Crossing the Valley of Death

THE TRANSLATION GAP

NIH research project grants by degree of principal investigator

PhD

MD

MD-PhD

Number of awards


Pharmaceutical industry spending and output

R&D expenditure

Indexed to 1996 value (% change)

New molecular entity output

Source: NIH; CMR International & IMS Health
Big Pharma and the Valley of Death
Development

Clinical Pharmacology & Therapeutics (2010); doi:10.1038/clpt.2009.293

Deconstructing the Drug Development Process: The New Face of Innovation

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Abstract

Forged in the early 1960s, the paradigm for pharmaceutical innovation has remained virtually unchanged for nearly 50 years. During a period when most other research-based industries have made frequent and often sweeping modifications to their R&D processes, the pharmaceutical sector continues to utilize a drug development process that is slow, inefficient, risky, and expensive. Few who work in or follow the activities of the pharmaceutical industry question whether change is coming. They know that the pharmaceutical sector, as currently structured, is unable to deliver enough new products to market to generate revenues sufficient to sustain its own growth. Nearly all major drug developers are critically examining current R&D practices and, in some cases, considering a radical overhaul of their R&D models. But key questions remain. What will the landscape for pharmaceutical innovation look like in the future? And, who will develop tomorrow's medicines?
Deconstructing the Drug Development Process: The New Face of Innovation

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Deconstructing the Drug Development Process: The New Face of Innovation

**Figure 1** Clinical development times (from IND filing to NDA submission) and regulatory approval times (from NDA submission to approval) for new molecular entities approved by the US Food and Drug Administration during the 5-year period 2003–2007, grouped by therapeutic area. Analysis by the Tufts Center for the Study of Drug Development, based on data included in its approved products database. *Note that the anti-infectives category excludes AIDS antiviral agents. IND, investigational new drug application; NDA, new drug application.

**Figure 2** New drug approvals (dots), represented on the left vertical axis, and pharmaceutical R&D expenditures (shaded area), represented on the right vertical axis, in the United States from 1963 to 2008. R&D expenditures are presented in terms of constant 2008 dollar value. The trend line is a 3-year moving average. The source of drug approval data is the Tufts Center for the Study of Drug Development (CSDD). The source of R&D expenditure data is the Pharmaceutical Research and Manufacturers of America; Industry Profile 2009; conversion of actual expenses to constant dollars was performed by Tufts CSDD.
Deconstructing the Drug Development Process: The New Face of Innovation

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$^a$US sales only.

Deconstructing the Drug Development Process: The New Face of Innovation

Figure 4  Market capitalization of top-tier pharmaceutical companies in January 2001 and September 2009. Cumulative loss in market capitalization for these companies over the period is $626 billion. Ticker symbols are as follows: ABT, Abbott; AZN, AstraZeneca; BMY, Bristol-Myers Squibb; GSK, GlaxoSmithKline; LLY, Lilly; MRK, Merck; PFE, Pfizer; SGP, Schering-Plough; WYE, Wyeth. Data from http://www.valueline.com; Tufts Center for the Study of Drug Development analysis.
They desperately need new tools and interventions.

**THE CHALLENGE OF NEGLECTED DISEASES**
Neglected diseases, neglected populations
Kimalel Health Centre, Ministry of Health of Kenya, a KEMRI-DNDi partnership
http://picasaweb.google.com/cmmorel/20090620To25Kenya#
Global diseases

Most neglected diseases

Neglected diseases

World pharmaceutical market
more than $400 bn in 2002
Malaria: the challenge

- People at risk of malaria: > 2 billion
- Malaria cases each year: 500 million
- Malaria deaths each year: 1 million
From the circumsporozoite protein to the RTS, S/AS candidate vaccine

Joe Cohen, Victor Nussenzweig, Ruth Nussenzweig, Johan Vekemans and Amanda Leach

1GlaxoSmithKline Biologicals; Belgium; 2Department of Pathology; Langone New York University Medical Center; NY USA

Key words: malaria, vaccines, RTS,S, adjuvant systems, Plasmodium falciparum, circumsporozoite protein
Critical scientific breakthroughs of the 1960s-70s

**Protective Immunity produced by the Injection of X-irradiated Sporozoites of* Plasmodium berghei**

R. S. Nusenzweig, J. Vanderberg, H. Most & C. Orton

Department of Preventive Medicine and Department of Radiology, New York University School of Medicine.

STUDIES with avian malaria have shown that killed sporozoites as well as sporozoites inactivated with ultraviolet light can produce a partial immunity after injection into birds. On the other hand, attempts to use the erythrocytic stages of the parasite as the source of antigen have met with only limited success with avian, rodent and monkey malaria. Previous attempts to use killed sporozoites of the rodent malarial parasite, *Plasmodium berghei*, to immunize rodents have been unsuccessful. We therefore sought to determine whether protective immunity to this parasite could be achieved by partial inactivation of the injected sporozoites as opposed to injection of dead parasites. X-irradiation was chosen as the inactivating agent, because of the partial immunity obtained by vaccination with irradiated blood forms of malaria parasites. This communication reports preliminary results on the production of protective immunity in mice by vaccination with X-irradiated sporozoites of *P. berghei*.

**Immunization of man against sporozite-induced falciparum malaria**

DAVID F. CLYDE
HARRY MOST
VINCENT C. MCCARTHY
JEROME P. VANDERBERG

American Journal of the Medical Sciences, 266:169-177, 1973
Scientific breakthroughs – 1980s’

Identification and chemical synthesis of a tandemly repeated immunogenic region of *Plasmodium knowlesi* circumsporozoite protein

G. N. Godson*, J. Ellis*, P. Svec*, D. H. Schlesinger† & V. Nussenzweig‡

* Department of Biochemistry, † Department of Medicine and Cell Biology, ‡ Department of Pathology, New York University Medical Center, 550 First Avenue, New York, New York 10016, USA

Rationale for the Development of an Engineered Sporozoite Malaria Vaccine

VICTOR NUSSENZWEIG* and RUTH S. NUSSENZWEIG†

*Department of Pathology and Kaplan Cancer Center, and †Department of Medical and Molecular Parasitology, New York University Medical Center, New York, New York 10016
Technological developments

• 1984: GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR) entered into a Collaborative R&D Agreement to produce a malaria vaccine using genetic engineering techniques and expression systems developed at GSK
  – End of 80s, early 90s: widespread disappointment
  – Early 80s: GSK Hepatitis B recombinant vaccine produced in yeast
HEPATITIS B SURFACE ANTIGEN AS CARRIER MATRIX FOR THE REPETITIVE EPITOPE OF THE CIRCUMSPOROZOITE PROTEIN OF PLASMODIUM FALCIPARUM.

Tineke Rutgers, Daniel Gordon\textsuperscript{2}, Anne Marie Gathoye, Michael Hollingdale\textsuperscript{3}, Wayne Hockmeyer\textsuperscript{2}, Martin Rosenberg\textsuperscript{1} and Michel De Wilde.

Department of Molecular Genetics, Smith Kline—RIT, 89 rue de l’Institut, B-1330 Rixensart, Belgium. \textsuperscript{1}Smith Kline and French Laboratories, 1500 Spring Garden street, Philadelphia, PA 19101. \textsuperscript{2}Department of Immunology, Walter Reed Army Institute of Research, Washington DC 20307. \textsuperscript{3}Biomedical Research Institute, Rockville, Maryland 20852. *Present address: Praxis Biologics, Inc., Rochester, New York 14623.
Technological breakthrough: RTS,S malaria vaccine candidate

- Faced with turning the repeating fragment from the protein into a real vaccine, Cohen decided to use lessons that the company had learned from its successful development of a recombinant hepatitis B vaccine, Engerix-B.

- That vaccine consisted of a surface antigen protein from hepatitis grown in yeast; at high enough concentrations that protein spontaneously forms virus-like particles that have a greater effect on the antibody-making parts of the immune system than loose proteins could.

- Fusing the repeat region from the CSP to the hepatitis surface antigen protein, Cohen hoped, would make similar particles festooned with the CSP fragments and thus able to provoke the production of antibodies targeted at the sporozoites.
Technological breakthrough: RTS,S malaria vaccine candidate

- Given a widespread suspicion that antibodies wouldn't be enough to elicit immunity, Cohen went on to add a fragment from the tail end of the CSP that was thought likely to interest the other arm of the immune system — the arm that prompts **T cells** to attack infected cells.
- The resultant “double whammy”, as Cohen calls it, was a gene for a protein containing the antibody-inducing **repeat (R)**, the portion recognized by **T cell** white blood cells (**T**) and the hepatitis B **surface** antigen (**S**).
- With all these additions, though, the surface antigen protein lost its knack for self assembly. Through a lot of fine tuning, Cohen finally hit on a way to regain it: one part RTS to four parts plain old S.
- RTS,S was born.
Technological breakthrough: RTS,S malaria vaccine candidate

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- RTS,S was born.
A critical development: a new adjuvant system

Development of RTS,S/AS02: a purified subunit-based malaria vaccine candidate formulated with a novel adjuvant

Nathalie Garçon†, D Gray Heppner and Joe Cohen

During the past decade, tremendous progress has been made in process development allowing for the production of large quantities of recombinant antigens, as well as in the understanding of the immune mechanisms underlying protection. Parallel to this, various and numerous adjuvant systems have been developed and tested in animal models and in clinical trials but have rarely induced protection. This review will discuss the development of a new adjuvant system (AS02) in combination with a malaria vaccine antigen candidate. To date, this vaccine is the only one to demonstrate protection in man in artificial challenge as well as in natural field trials. It has been established that this adjuvant system is capable of eliciting high antibody titers along with strong cell-mediated immunity which both contribute to the efficacy of the vaccine.

The World Health Organization, PATH MVI, the Bill & Melinda Gates Foundation and the Wellcome Trust, together with representatives of the European and Developing Countries Clinical Trials Partnership (EDCTP), the European Malaria Vaccine Initiative (EMVI), the European Commission (Directorate General for Research), the United States National Institute for Allergy and Infectious Diseases (NIAID), and the United States Agency for International Development (USAID) form part of a *malaria vaccine funders' group*, with the WHO Initiative for Vaccine Research as its focal point. The group's participation and support was critical to the Roadmap process.
Public-Private Partnerships support large-scale clinical trials of RTS,S

• PATH (Program for Appropriate Technology in Health) Malaria Vaccine Initiative (MVI) and GlaxoSmithKline (GSK) Biologicals, in collaboration with Africa-based research institutions, have completed Phase 2 clinical trials of GSK’s candidate vaccine RTS,S in Mozambique, Tanzania, Gabon, Ghana, and Kenya.

• A large-scale Phase 3 trial—the last stage of development before the vaccine is submitted to regulatory authorities—was launched in May 2009. That trial includes additional sites in Burkina Faso, Kenya, and Malawi.
RTS,S Clinical Research Center Network
(source: Christian Loucq, MD Director, PATH Malaria Vaccine Initiative)
Hard work, collaboration and critical breakthroughs generated a robust candidate malaria vaccine

- **Scientific breakthroughs**
  - Research findings
  - New science of molecular biology
- **Technological breakthroughs**
  - Hepatitis B virus-like proteins & CSP protein
  - New adjuvants
- **Management and financial breakthroughs**
  - Partnerships for Product Development (PDPs)
  - Malaria vaccine funders’ group (WHO/IVR)
Innovation, intellectual property rights, prices, and policies

ACCESS, ACCESS, ACCESS
What will be needed if a new drug or vaccine a comes through? Answer: ACCESS

“We live in an extraordinary time in the history of public health: never before has the world had such powerful technologies to fight disease and improve lives. Yet medical breakthroughs mean little if they fail to reach those in greatest need. Today, millions of people in the poorest countries do not have access to effective vaccines, medicines, and other life-saving tools (...)

I am hopeful that in the coming years, the speed of improvements in global health will continue. With dedication and ingenuity, we can create a world in which all people have access to the tools they need to live healthy, productive lives.”

Tadataka Yamada, M.D.
President, Global Health Program
Bill & Melinda Gates Foundation

http://www.accessbook.org
A Global Strategy and a Plan of Action

Global strategy and plan of action on public health, innovation and intellectual property

The Sixty-first World Health Assembly,

Having considered the report of the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property;¹

Recalling the establishment pursuant to resolution WHA59.24 of an intergovernmental working group to draw up a global strategy and plan of action in order to provide a medium-term framework based on the recommendations of the Commission on Intellectual Property, Innovation and Public Health, and to secure, inter alia, an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area;

Recalling resolutions WHA49.14 and WHA52.19 on revised drug strategy, WHA53.14 and WHA54.10 and WHA57.14 on HIV/AIDS, WHA56.27 on intellectual property rights, innovation and public health, WHA58.34 on the Ministerial Summit on Health Research, WHA59.26 on international trade and health, and WHA60.30 on public health, innovation and intellectual property;

Welcoming the progress made by the Intergovernmental Working Group in elaborating the global strategy and the identification of the stakeholders in the plan of action,

1. ADOPTS the global strategy and the agreed parts of the plan of action on public health, innovation and intellectual property, attached to this resolution;
Be coherent on access and delivery

“...encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation, especially to meet the R&D needs of developing countries, protects public health and promotes access to medicines for all, as well as explore and implement, where appropriate, possible incentive schemes for R&D”
From TRIPS-Minus, to TRIPS, to TRIPS-Plus

• “...during the past few years, a number of countries have adapted and incorporated more enhanced levels of IPR protection unwillingly as a result of pressures exerted on them by the industrialized countries, either under the WTO or under some bilateral free trade agreements. The latter trend was championed by the United States and the European Union in their latest free trade and association agreements...”

5. Coherence: The above-mentioned principles should apply to all EU policies which directly or indirectly affect health in the EU and non-EU countries. The main policies which will require special attention are development (of local capacity), mobility (mitigation of the effects of brain drain), trade (ensuring access to essential medicines for the poor) and research (equity of priorities on global health research and development of new medicines and measures).

Question 16: What are the keys to ensuring equitable access to medicine and how could the EU help to do more on this, including by supporting innovation and management of intellectual property rights?
Coherence? 

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**Intervention by Brazil at WTO General Council on seizure of 500 kilos of generic medicines by Dutch customs authorities**

Submitted by thiru on 3. February 2009 - 14:08

Brazil  WTO  India  The Netherlands  Other country trade disputes

On this day, 3 February 2009, H.E. Ambassador Roberto AZEVÊDO, Permanent Representative of Brazil to the World Trade Organization (WTO) and other economic organizations in Geneva made the following intervention at the WTO General Council meeting on the seizure by Dutch authorities of a cargo of 500 kilos of losartan potassium on route from India to Brazil.

An informed source notes that India and 16 other members of WTO including Argentina, Bolivia, Burkina Faso, China, Costa Rica, Cuba, Ecuador, Egypt, Indonesia, Israel, Nigeria, Peru, Pakistan, South Africa, Thailand and Venezuela supported Brazil’s intervention.
Dutch confiscation of HIV drugs for Nigeria threatening

Patent discord embarrasses EU and Clinton foundation

Dozens of HIV patients have been placed at risk after the Dutch authorities seized consignments of Indian-made medicines shipped via Schipol airport for distribution to clinics in Nigeria, a multilateral agency on Wednesday said.

Officials claimed the drugs were counterfeits and violated patent rules but Unitaid, the Geneva-based agency which paid for the medicines, demanded their release and said the claims were "misleading".

The action - the latest seizure of drugs shipped via the Netherlands to developing countries - has highlighted tensions between European Union legislation and special patent rules on medicines agreed by the World Trade Organisation, which on Wednesday offered to intervene in the dispute.
Industrialized countries: Two options ahead
Drug reforms and ambulatory care initiatives in Sweden

• Three principles
  – Swedish residents should have equal access to high-quality care, irrespective of their status and income
  – Patients in greatest need take precedence
  – Treatment choices should consider both costs and outcomes

2002: Mandatory generic substitution

- Only the cheapest substitutable product available in the community pharmacy is reimbursed
- *Medical Products Agency* reviews and decides which products are substitutable

Limiting pharmaceutical company activity

- National agreements signed between *Swedish Association of Pharmaceutical Industries* and the *Swedish Medical Association* limiting contact with physicians and healthcare professionals

- Funding for attending congresses changed with funding for travel and accommodation divided between councils and companies

Factors influencing pharmaceutical expenditure (Godman et al, 2009)

Intellectual property rights and innovation in developing countries

Fig. 2. A scatter plot of the relationship between IPRs and per capita GDP.

Intellectual property rights and innovation in developing countries


Kernel regression, bw = .5, k = 6

IP protection due to external pressure
IP policy in transition
IP protection due to country’s decision

Fig. 3. Semiparametric estimates of the effect of GDP per capita on IPRs.

Brazil’s policy on intellectual property: opinion of a multinational CEO

- "A decisão de investir no Brasil reflete a estabilidade e previsibilidade política e jurídica do país, a existência de forte lei de propriedade intelectual, sólidas políticas de saúde na área de prevenção de doenças com um programa de imunização reconhecido como um dos melhores do mundo, além de uma agência reguladora pré-qualificada pela Organização Mundial de Saúde (OMS) para suporte a planos de exportação”

- “The decision to invest in Brazil reflects the stability and the legal and political predictability of the country, the existence of a strong law protecting intellectual property, solid health policies on disease prevention based on an immunization program recognized as one of the best in the world, in addition to a WHO pre-qualified regulatory agency to support export plans”

Source: Valor Econômico, August 26, 2010
Thank you

*Muito obrigado*

morel@cdts.fiocruz.br