EASL and Liver Research at the European Leve
The viRgil network of excellence

VIRGIL: COMBATING RESISTANCE TO ANTIVIRAL TREATMENTS

April 17, 2005
EASL, Paris

Fabien Zoulim
INSERM Unit 271, Lyon

Sixth Framework Progra

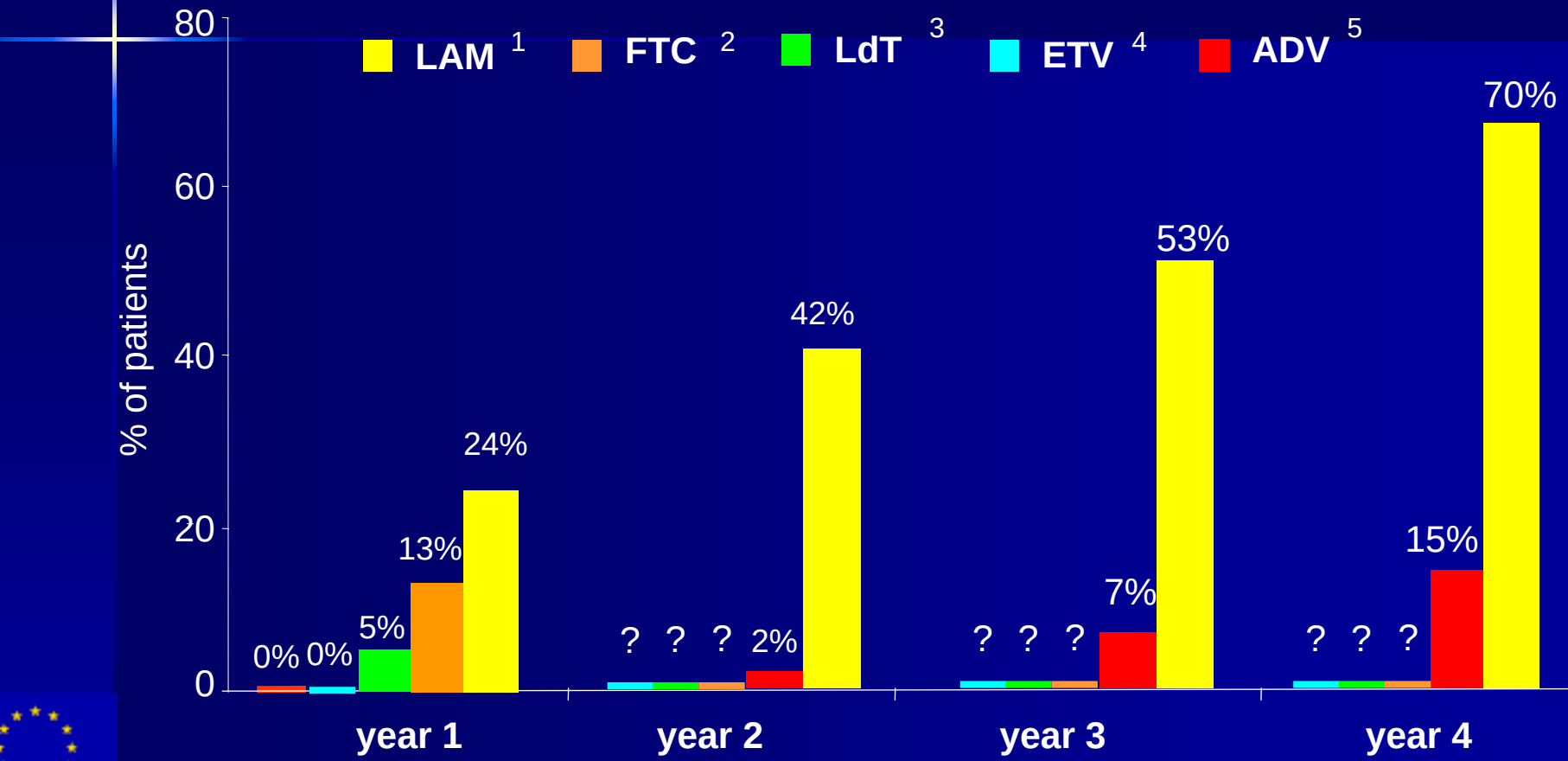
General Objectives

TO ORGANISE THE EUROPEAN FIGHT AGAINST VIRAL DRUG RESISTANCE WITH A COMPREHENSIVE AND INTEGRATED ULTRASTRUCTURE

MODEL: 3 major viral diseases in Europe

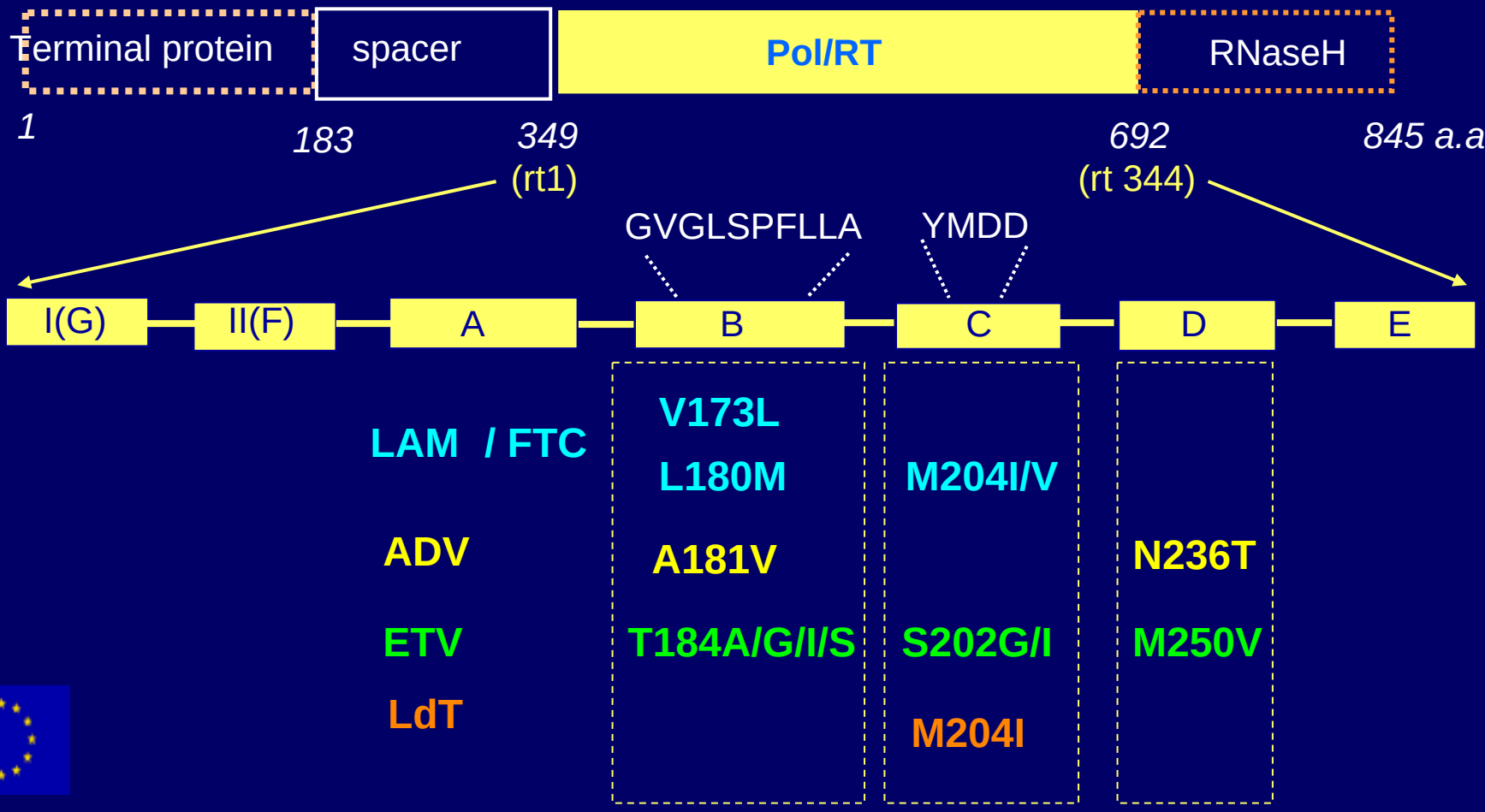
- **Influenza**
  - **Annual epidemic outbreaks**
    - **114 000 hospitalizations / year**
    - **21 000 Deaths / year**
  - **Anticipation for pandemic planning and viral resistance**
- **Chronic hepatitis**
  - **Hepatitis B**
    - **15 million chronic carriers in Europe**
  - **Hepatitis C**
    - **8-10 million chronic carriers in Europe**
  - **Responsible for 2/3 of cirrhosis and liver cancer**
  - **Treatment failure:50-60% patients**

HBV resistance to therapy



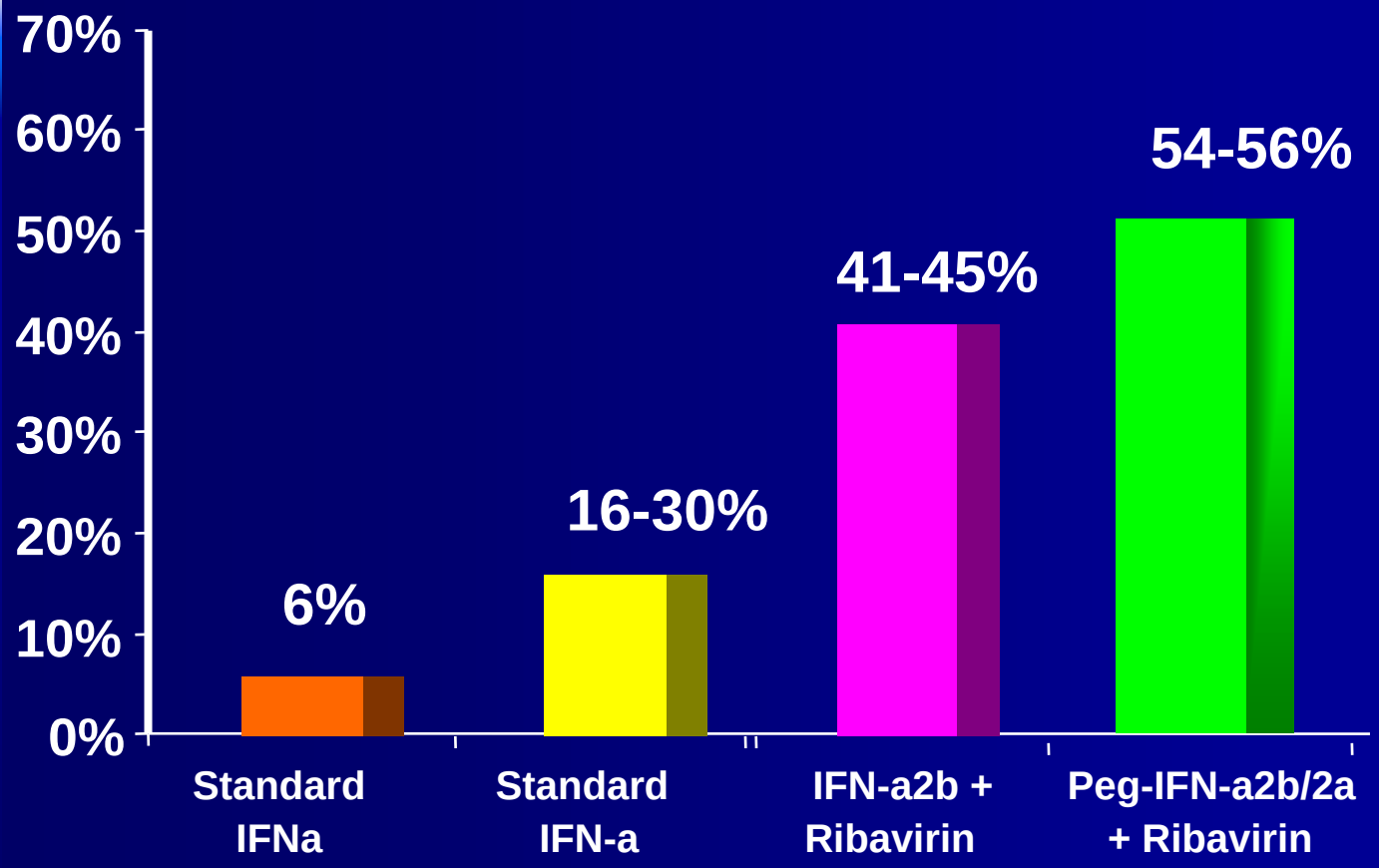
1 Lai et al. Clin Infect Dis. 2003;36:687-96
2 Schiffman ML et al. Hepatology 2004; 40:172A
3 Lai CL, et al. Hepatology 2003; 38: 262A
4 Colonno RJ, et al. Hepatology 2004; 40: 661A
5 Xiong et al. EASL 2005
6 Angus et at Gastroenterology (2003)
7. Villeneuve et al J. Hepatol.

HBV resistance to nucleoside analogs



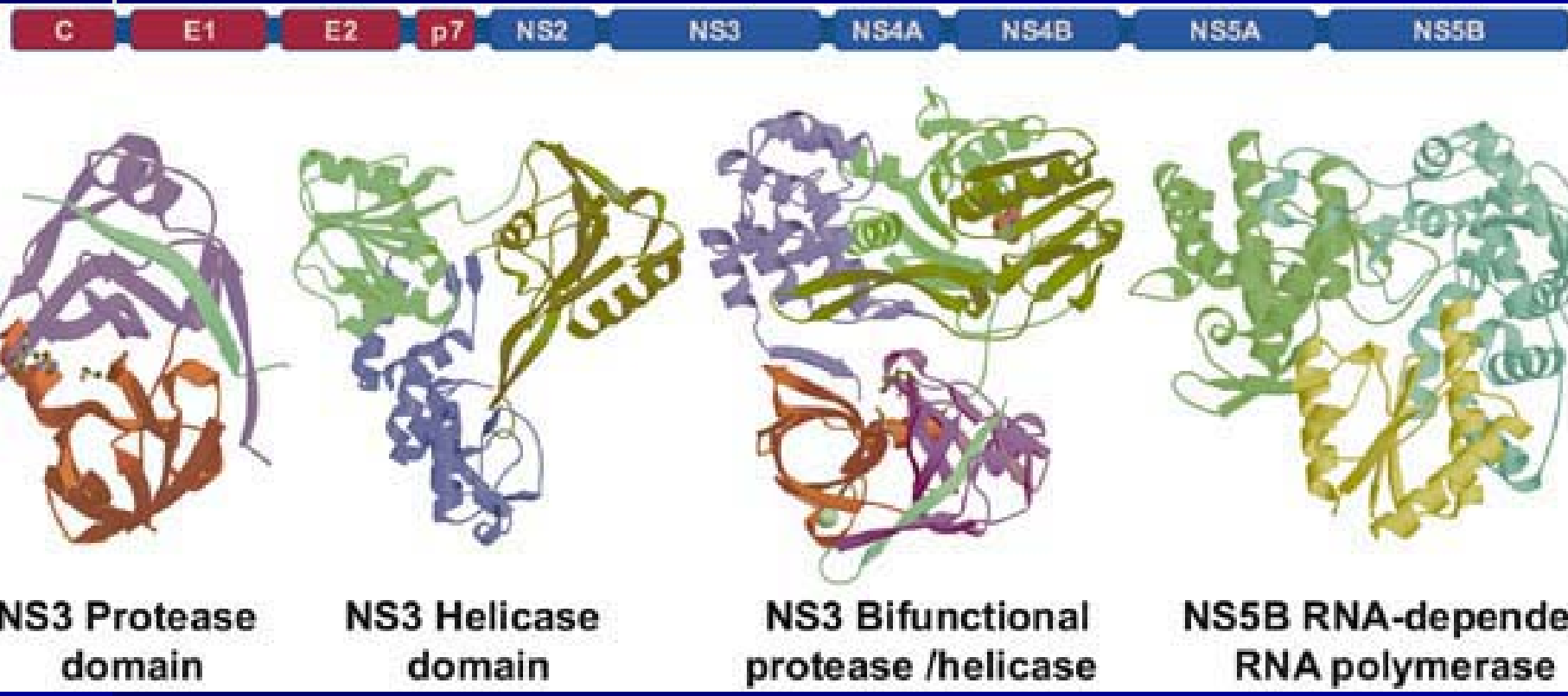
Allen Hepatology 1998, Delaney J Virol 2003, Angus Gastroenterology 2003,

Chronic hepatitis C Treatment response and failure



Manns, Lancet 2001; Fried NEJM 200

HCV : the new targets and the resistance problem



Di Bisceglie et al., Hepatology 2002

Specific Objectives

- Improve the understanding, diagnosis, surveillance, and treatment of antiviral drug resistance
- Improved benefit/cost of viral disease management
- Integration of European research excellence and capacities

viRgil Network
A European Coverage

viRgil Network composition

12 European Member States
55 institutions

Steering Committee
Project Management Team

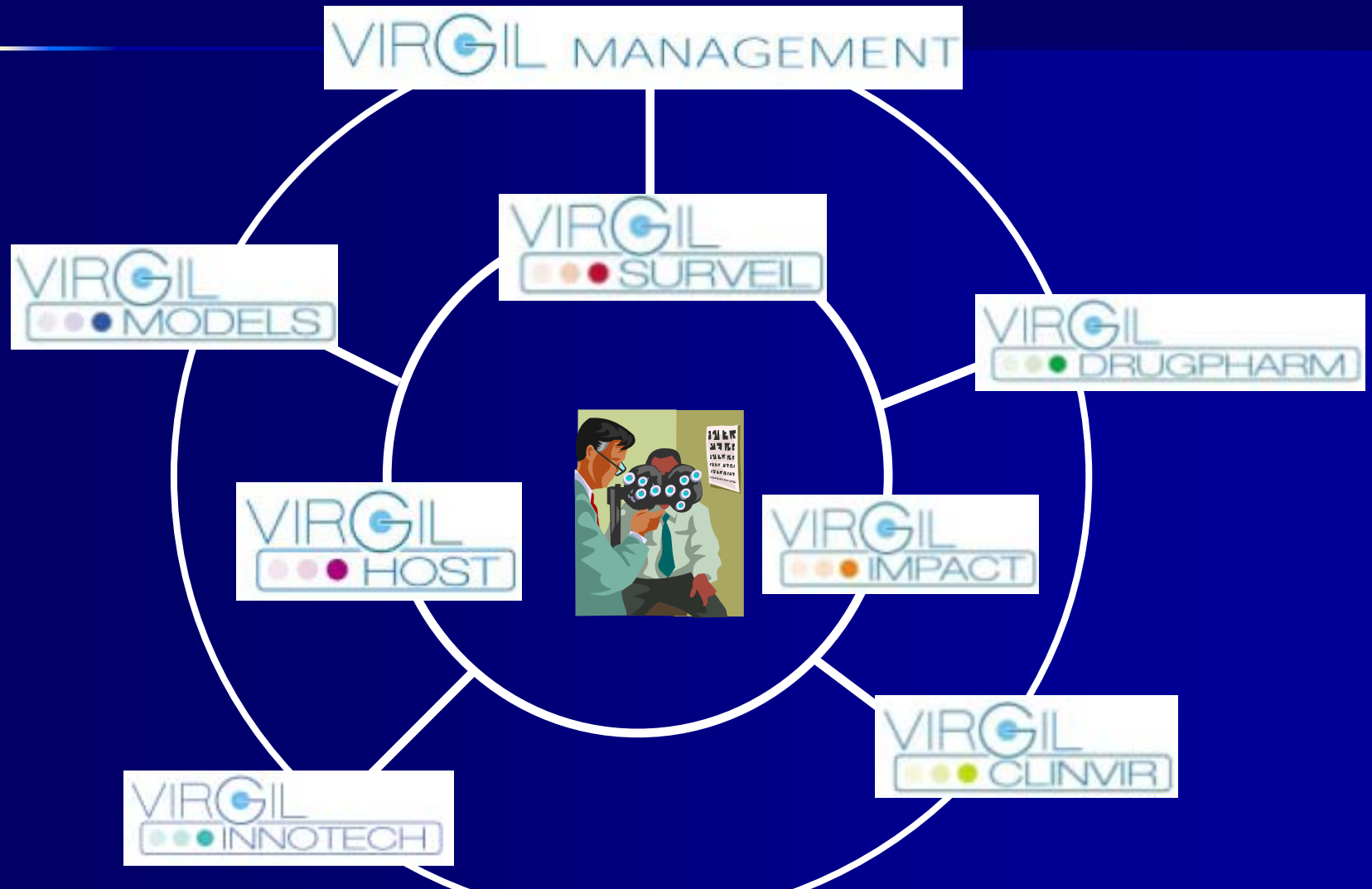
60 scientific teams

7 Pharmaceutical companies / Biotech
- Bioalliance
- BioMérieux
- LiverDoc
- Retroscreen
- Riotech
- Tripep

Governing Board
Scientific Advisory Board
Patients Advocay Groups

EC grant for integration:
9 M € / 4 years

viRgil Network
The structure



Major strengths

- Complementarity/Excellence of the teams
- Exchange of material, expertise, personel
- Centralized platforms for collaborative clinical and pre-clinical studies
  - New drugs
  - New assays
- > Integration of activities
- > More ambitious and larger scale projects
- > Additional grants

Launching of viRgil activities

- Kick-off meeting, June 27-29, 2004 in Lyon
  - Launching at the Rhône-Alpes region council headquarters
  - Press conference
  - Internal meeting with the network members
- Management structure in place
- Website in place: **http://www.virgil-net.org/**
  - Intranet
  - Extranet
  - Links with scientific societies (EASL, national liver societies, etc...)

ViRgil launching Lyon, June 27-29

Forschung

Erstes europäisches Netzwerk zu Hepatitis und Influenza

Es ist das erste Forschungsnetz (network of excellence), das die Europäische Union im 6. Rahmen-

förderungsprogramm mit mehr als neun Mio. € fördert: ‚Virgil' steht für ‚Vigilance against Viral Resistance' und soll vier Jahre lang die europaweite Forschung zu Hepatitis B und C sowie zur Influenza bündeln. Im Augenmerk der Wissenschaftler sind so genannte Resistenzen: Bei einigen Viren wirken bislang erfolgreiche Medikamente nicht mehr, die Erkrankungen breiten sich dadurch wieder

55 medizinische Organisationen und sieben Firmen aus zwölf europäischen Ländern sind an ‚Virgil' beteiligt. Koordiniert wird das gesamte Netzwerk vom Institut National de la Santé et de la Recherche Médicale (Inserm), Paris, Frankreich.
www.virgil-net.org

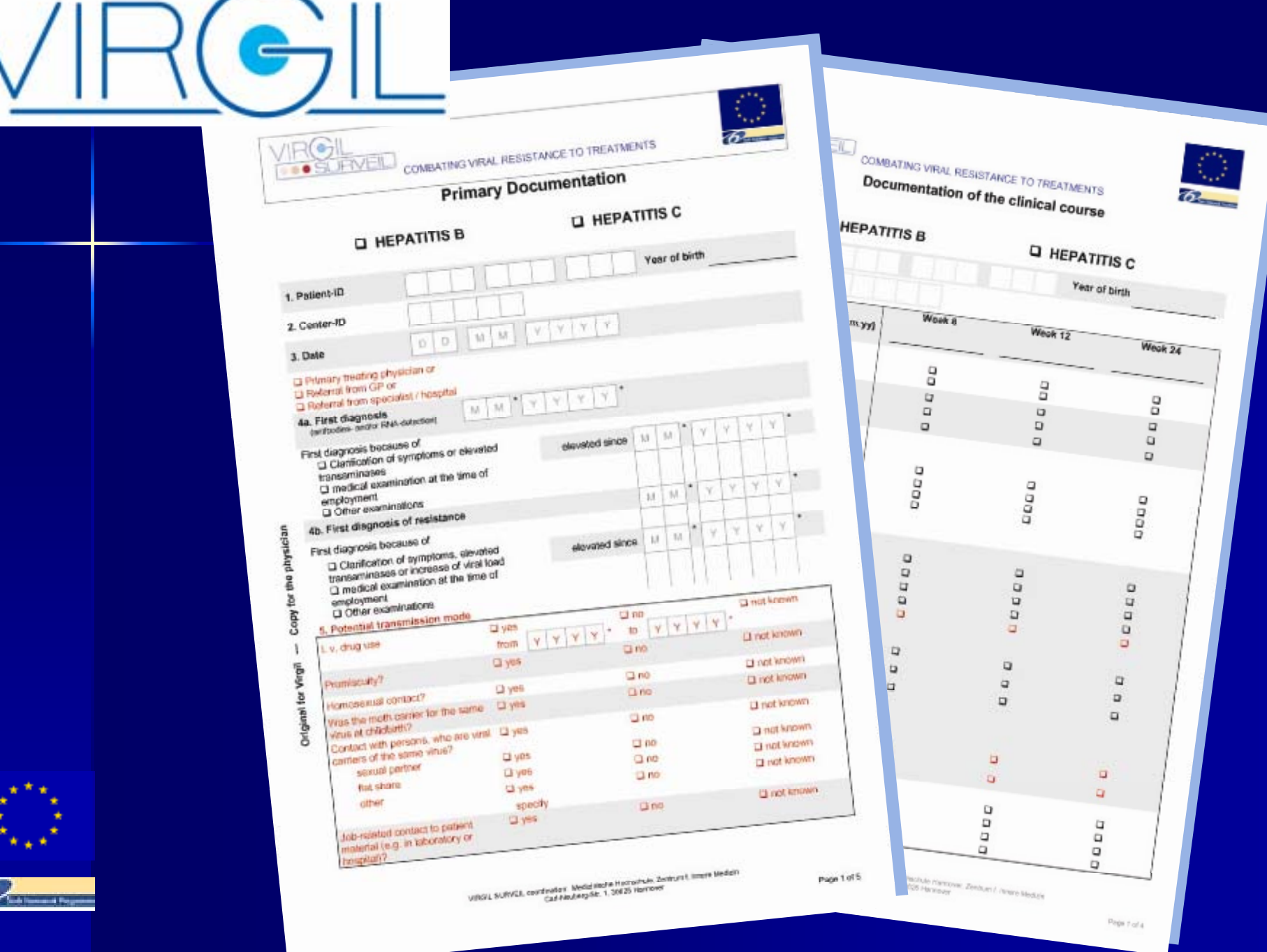
Beim Virgil-Kick-off-Meeting vom 28. bis 30. Juni 2004 in Lyon (v. l.): Dr. Jerome Weinbach (Projektmanager, Inserm Transfert Paris), Prof. Fabien Zoulim (Koordinator des Gesamtnetzes Virgil, Inserm Transfert Paris), Prof. Michael P. Manns (Projektkoordinator der Themenplattform Virgil-Surveil, Direktor der Abteilung für Gastroenterologie, Hepatologie und Endokrinologie der MHH) und Dr. Thomas

The basis for clinical research

- Common definition of viral drug resistance
- Common clinical record form to
  - Collect clinical data
  - Collect samples for further biological studies
  - Identify patients for clinical studies

viRgil definition of viral drug resistance

	ÒprimaryÓtreatment failure*	ÒsecondaryÓtreatment failure *
Hepatitis B	decline of HBV-DNA load in serum < 1log10 IU/ml after 12 weeks of therapy compared to baseline value.	increase in viral load in serum durin therapy of at least 1log10 IU/r compared to the nadir value
Hepatitis C	1. decline < 2-log (IU/mL) of HCV RNA load in serum at week 12 of therapy in comparison to baseline value. 2. Patients with further treatment until week 24 (Òslow responderÓ) are considered as non-responders if they are not HCV RNA negative in serum at week 24.	at least 1-log increase of viral loa (IU/mL) in serum determined at t w different time points during IFN-base therapy after initial response.


VIRGIL
COMBATING VIRAL RESISTANCE TO TREATMENTS
Primary Documentation
HEPATITIS B
HEPATITIS C
Year of birth
1. Patient-ID
2. Center-ID
3. Date
Primary treating physician or
Referral from GP or
Referral from specialist / hospital
4a. First diagnosis
First diagnosis because of
Clarification of symptoms or elevated transaminases
medical examination at the time of employment
Other examinations
elevated since
4b. First diagnosis of resistance
First diagnosis because of
Clarification of symptoms, elevated transaminases or increase of viral load
medical examination at the time of employment
Other examinations
elevated since
5. Potential transmission mode
i. v. drug use
Promiscuity?
Homosexual contact?
Was the moth carrier for the same virus at childbirth?
Contact with persons, who are viral carriers of the same virus?
sexual partner
flat share
other
Job-related contact to patient material (e.g. in laboratory or hospital)?
yes
no
not known
from
to
specify
Original for Virgil — Copy for the physician
VIRGIL SURVEIL coordination: Medizinische Hochschule, Zentrum f. innere Medizin
Carl-Neuberg-Str. 1, 30625 Hannover
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COMBATING VIRAL RESISTANCE TO TREATMENTS
Documentation of the clinical course
HEPATITIS B
HEPATITIS C
Year of birth
Week 8
Week 12
Week 24

viRgil ready to start clinical studies !

- Ongoing activities of the centralized platforms
- Implementation of a clinical trial platform for European trials

-> European clinical research infrastructure network (ECRIN)

- Endorsement of viRgil activities by the EASL

VIRGIL Doc

Follow up

Best practice

Physician

Patient

Physician

Consultation request

Report

Decision Support System

Liver Expert

Database

Dissemination of knowledge activities

- Endorsement/organization of several meetings
  - 2004: Immunology, HBV, & HCV (Heidelberg) meetings
  - 2005: HBV meeting (Heidelberg)
  - 2005: « virology of hepatitis B » book
  - 2005: Virgil antiviral drug resistance symposium (Lyon), BioVision

VIRGIL International Workshop on Antiviral Drug Resistance

http://www.virgil-net.org/

June 8, 2005

Lyon, France

Dissemination of knowledge

- Interaction between partners
  - Exchange of material / methodology
  - Exchange of scientific personel
  - Start of new collaborative studies
- Interaction with other European actions
  - Biosapiens network
  - ECRIN
- Already > 20 viRgil publications and patent applications

-> Infrastructure for clinical research on drug resistance

TH FRAMEWORK
OGRAMME

Institut national
de la santé et de la recherche médicale

RHÔNE-ALPES
LA RÉGION

E A
S L

60 teams & 55 institutions

VIRGIL MANAGEMENT

J Weinbach, PM
INSERM-transfert
F Zoulim, coordinato
INSERM

R Bartenschlager
A Hay

VIRGIL MODELS

VIRGIL SURVEIL

M Manns
B Lina

VIRGIL DRUGPHARM

J Neyts

G Pape
S Ludwig

VIRGIL HOST

VIRGIL IMPACT

S Schalm
JM Cohen

VIRGIL CLINVIR

JM Pawlotsl
M Zambon

VIRGIL INNOTECH

W Spaan
J Oxford