The Human Metagenome Project – Recommendations from the Paris Workshop

A detailed understanding of human biology will require not only knowledge of the human genome but also of the human metagenome (1, 2). Humans live in constant association with microbes that are present on surfaces and in cavities of the human body, and even within our cells. The number of our microbial companions exceeds by at least ten-fold those of cells of our own body and the number of unique genes they encode is at least 100-fold greater than the number of genes in our own genome (3, 4). This complex and dynamic microbiota has a profound influence on physiology, nutrition, immunity and development and disruptions in these human-associated microbial communities are a significant factor in many diseases (5-8).

Understanding the dynamic and variable nature of human microbial communities is a critical aspect of the challenge before us. Defining this dynamic diversity represents the next frontier of genomics. The goal of the Human Metagenome Project is to characterize the human microbiota, enabling the study of its variation with population, genotypes, disease, age, nutrition, medication and environment, and therefore opening avenues to modify it to optimize the health and well-being of any individual.

Sequencing of the genomes of plants, animals, and microbes has revolutionized biology and medicine, providing an in-depth sketch of the biological potential of each organism. However, the genomic content of our resident microbial community is largely unknown due to the inability to identify and culture a large percentage of these microbes. Metagenomics is a relatively new and powerful approach to study the genomes of all microbes in an ecological niche. In metagenomics, the microbial population is extracted from the niche, the DNA is purified, and, using high throughput shotgun cloning techniques, the entire sample is sequenced. From such data, the presence of genes of both cultured and currently uncultured microbes can be deduced and even the entire genomes can be reconstituted. Proof that metagenomics can produce useful data has recently been shown (9-11).

Distinct sets of organisms are found in different human body sites. Characterization of the microbiota from each of these sites is needed in order to compare and contrast the microbial communities and to understand how they contribute to human health and disease. Initial work is already underway to elucidate complexities of communities in the oral, intestinal and genital tract. A bold new initiative to fully characterize one of these sites, the gastrointestinal tract, was proposed at a INRA-sponsored conference in Paris, October 28-29. This characterization would represent considerable progress towards deciphering the entire human metagenome, as the GI tract contains a particularly rich microbial community, composed of bacteria, archaea, eukaryotes and viruses.

The Human Intestinal Metagenome Initiative

The primary objective of the Human Intestinal Metagenome Initiative (HIMI) is to develop a reference set, corresponding to the genetic repertoire of the intestinal microorganisms. For this purpose it aims 1) to sequence the complete genomes of cultured microorganisms from the GI tract; 2) to develop and apply methods to sequence genomes of currently uncultured microorganisms and 3) to generate a genetic catalogue directly from the whole community. This reference set will enable, enhance and accelerate studies of the role that intestinal microbiota play in health and disease and will lead to new and unexpected biological insights into human biology and human interactions with the environment.

Firstly, the reference set will provide a detailed view of the diversity of intestinal microorganisms and of the functions they encode. There is a very high probability that as yet unknown microbes will be identified, genetic fluxes and metabolic networks will be deduced, intestinal metabolic fluxes will be better understood, new detoxification pathways will be detected and novel bioactive compounds (peptides, enzymes, antimicrobials) will be discovered.
Secondly, the reference set will enable the development of tools, such as micro-arrays, permitting rapid in-depth visualization of microbial communities. These tools will allow investigations of microbial variation, in terms of microbial and gene content, as well as gene expression, within and between human populations and cohorts. They should reveal correlations between the composition and/or physiology of the intestinal microbiota and the state of health of an individual. Similarly, they should detect associations between specific genes, microbes, changes in microbial composition and/or physiology and different human pathologies. Associations that are highly suspected, although potentially only indirectly mediated by the action of bacterial metabolites, are with colon cancer, diabetes and autism. The tools should facilitate the development of new diagnostics, based on altered microbial community profiles associated with a variety of chronic diseases, such as Irritable Bowel Syndrome, Inflammatory Bowel Disease, allergic conditions, and obesity. They should also lead to the development of prognostic signatures for predicting disease and responses to therapeutics, a better understanding of metabolism of drugs and also of xenobiotics. The results are expected to stimulate innovation and product development in the pharmaceutical industry, leading to the synthesis of more specific preventative and therapeutic drugs, with fewer side effects, as well as in the food and food ingredients industries. New products for food ingredients and dietary supplements will come in the areas of: soluble fibers, enzymes, and microbial cultures. The metagenome initiative will create a rational foundation for the area of "Functional Food". Through the tools developed it will become possible to assess the impact of any food on the intestinal flora. This will have a large impact on innovation in the entire food industry. The innovation arising from the initiative will be exploited in the well-established industries, and most likely also stimulate the establishment of a variety of new companies.

Thirdly, the reference set will lead to the development of functional genomics of intestinal microbial communities, such as the characterization of new molecular signals and different forms of dialogue between community members and with their human host. An immunomodulatory molecule of a symbiotic microbe that directs the maturation of the immune system has recently been discovered (12), and further novel insights are expected on immunomodulatory functions of microbes both in the development of the immune system and conversely in immunosenescence. These efforts will also provide insights into the role of the gut microbiota as an immune adjuvant, which could affect vaccination strategies and optimization of live vaccines. They will open the way to reasoned intervention, on an individual basis, aimed at modifying the intestinal microbiota in order to promote health and well-being.

The International Metagenome Consortium

To reach the ambitious goals of the HIMI, a broad international consortium of laboratories and other concerned institutions will be constituted. The division of work, synergies and economies of scale that can be achieved through an international effort will decrease the cost and increase the speed of discovery, by enhancing the efficiency and minimizing the overlap of the effort. The Consortium will 1) allow standardization of procedures and quality control of the data; 2) coordinate the analyses and ensure the free and rapid flow of data and resources throughout the scientific community; 3) manage the reference data set and maintain its currency throughout all stages of development of the project.

An important role of the International Metagenome Consortium will be to promote and solicit funding for the Initiative at an international scale. To this end the Consortium will advocate and coordinate pooling of resources and expertise commensurate with the scale and complexity of the effort, which is likely to exceed that of the Human Genome Project. Indeed, the Initiative intends to sequence full genomes of approximately one thousand bacterial species, the total size of which is equivalent to that of the human genome (although likely to encode roughly 100-fold more genes), and to catalog by direct random sequencing of the intestinal microbial communities genes of several thousands more species, including archaea, bacteria, eukaryotes and viruses, equivalent to several more human genomes.

Another important goal of the Consortium will be to promote functional and comparative studies based on the Intestinal reference genetic repertoire. These studies are highly synergistic
with the primary goal of the Initiative. The Consortium will also provide encouragement and help for initiating projects to generate the genetic repertoire of microbiota from other sites of the human body, crucial for the full characterization of the Human Metagenome.

The Consortium will be constituted of Members committed to: 1. contribute work required to generate the data; 2. carry out the analyses of the data; 3. contribute the necessary funds and 4. abide by the rules agreed to by the Consortium, particularly rapid unconstrained release of the data into the public domain. It will additionally set up Working Groups that will deal with issues central to the program:

1. Genome prioritization working group-- will produce a prioritized list of genomes of cultured intestinal microorganisms and update the list in response to the accumulation and analysis of data. It will serve as a clearing house to coordinate the sequencing of the genomes and avoid duplication of effort among the members of the Consortium. It will help define the sampling procedures that will lead to the broadest catalog of genome sequences from the presently uncultured microorganisms and steer the sampling as the program unfolds to optimize the catalog. It will define levels of sequence quality and completion for whole genome sequences, and depth of coverage for metagenomic sequences. It will promote exchange of techniques and technologies between sequencing centers.

2. Technology development working group-- will focus on development and application of techniques for sequencing the genomes of uncultured microorganisms from complex communities. The goal of these techniques will be to expand the number of full genome sequences well beyond that of the cultured intestinal microorganisms. They will provide the means to increase the sequence catalog of genomes from uncultured microorganisms.

3. Bioinformatics working group-- will focus on standardization of sequence annotation and on other bioinformatic issues, such as data organization, exchange and accessibility, which are critical for the optimal use of sequence information.

4. Biological resources working group -- will advise consortium members on the handling of the biological materials and resources, their maintenance and their flow within and out of the consortium.

5. Outreach working group-- will deal with issues of outreach such as ensuring that there is a good interface between the Consortium and the users of the generated resources including investigators from academia, medicine and industry, with the objective of accelerating discovery for the benefit of society. A number of industries have expressed their support and strong interest in the Intestinal Metagenome Initiative. In order to facilitate the contact between the consortium and relevant industries the Consortium intends to establish an Industrial Platform, open to interested companies, which will give advice to the Consortium. Regular Conferences for the members of the Industrial Platform will be organized, whereby the practical application of the results obtained will be inspired and facilitated. A distinct but related issue is presenting the goals and the results of the Consortium to the general public, to help develop an informed public perception of the Initiative’s expected impact on basic understanding of human health. Finally, this working group will actively promote funding of the activities of the Consortium on an international scale.

The Consortium will be initially established for five years. The activities of the Consortium will be coordinated by a Board, composed of the Coordinator, nominated representatives of the Members, elected representatives of the Working Groups and a representative of the Industrial platform. The Board will have the authority to undertake actions deemed necessary to establish the reference genetic repertoire set of the human intestinal microbiota, which is the primary goal of the Human Intestinal Genome Initiative. These actions will include, but are not limited to, drafting and amending the Consortium rules, inviting groups and individuals to become members of the Consortium, examining and granting the requests by groups and individuals to join the Consortium, terminating the membership in the Consortium for just cause, promoting funding of the Consortium activities, approving decisions and suggestions brought forth from the Working Groups and overseeing their implementation, promoting exchange of information within and
outside of the consortium by organizing appropriate meetings etc. The founding members of the
Consortium will elect the initial Board members. The initial Board members will be asked to
serve for 1.0 or 2.5 years while members appointed to replace the initial members will be asked
to serve for 2.5 years. This will allow for a regular rotation of members so that the entire Board
does not rotate off at one time. The Coordinator will be elected by the members of the Board for
2.5 years, renewable. The new Board members will be recruited following proposals by the
Coordinator, based on the suggestions emanating from the Working Groups, Consortium
members and Industrial Platform, for the same period.

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Appendix : List of participants
## List of Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>e-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas ALBERT</td>
<td>NimbleGen Systems Inc., One Science Court, Madison, WI 53711, USA</td>
<td><a href="mailto:talbert@nimblegen.com">talbert@nimblegen.com</a></td>
</tr>
<tr>
<td>Fabrizio ARIGONI</td>
<td>Ph.D - Nestlé Research Center P.O. Box 44 CH-1000 Lausanne 26 Switzerland</td>
<td><a href="mailto:fabrizio.arigoni@nids.nestle.com">fabrizio.arigoni@nids.nestle.com</a></td>
</tr>
<tr>
<td>Vasco AZEVEDO</td>
<td>Dept de Biologia Geral, ICB/UFMG Av. Antônio Carlos,6627, Pampulha,Belo Horizonte, Minas Gerais - Brazil.</td>
<td><a href="mailto:vasco@mono.icb.ufmg.br">vasco@mono.icb.ufmg.br</a></td>
</tr>
<tr>
<td>Sylvie BARDON</td>
<td>INRA, DS NHISA, 147, rue de l'Université 75007 Paris cedex 07 France</td>
<td><a href="mailto:sylvie.bardon@paris.inra.fr">sylvie.bardon@paris.inra.fr</a></td>
</tr>
<tr>
<td>Philippe BEAUNE</td>
<td>INSERM EMRC 490 Laboratoire de Biochimie Toxicologie Moléculaire, Centre universitaire des Saints-Pères 45 rue des Saints-Pères 75270 Paris cedex 06 France</td>
<td><a href="mailto:philippe.beaune@univ-paris5.fr">philippe.beaune@univ-paris5.fr</a></td>
</tr>
<tr>
<td>Jean-Baptiste BERGE</td>
<td>INRA, 147, rue de l'Université 75007 Paris cedex 07 France</td>
<td><a href="mailto:jean.berge@paris.inra.fr">jean.berge@paris.inra.fr</a></td>
</tr>
<tr>
<td>Peer BORK</td>
<td>European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, Germany</td>
<td><a href="mailto:borks@embl-heidelberg.de">borks@embl-heidelberg.de</a></td>
</tr>
<tr>
<td>Alain BULEON</td>
<td>INRA, Unité Biopolymères, Interactions, Assemblages Equipe Systèmes Assemblés Semi Cristallins BP 71627 44316 Nantes Cedex 3 - France</td>
<td><a href="mailto:buleon@nantes.inr.fr">buleon@nantes.inr.fr</a></td>
</tr>
<tr>
<td>Nadine CERF</td>
<td>INSERM EMRC 490 Faculté de Médecine Necker-Paris V 156, rue de Vaugirard 75730 Paris Cedex 15 - France</td>
<td><a href="mailto:cerf@necker.fr">cerf@necker.fr</a></td>
</tr>
<tr>
<td>Mike CHANDLER</td>
<td>CNRS, Laboratoire de Microbiologie et Génétique Moléculaires 118 route de Narbonne 31062 Toulouse - France</td>
<td><a href="mailto:miche.chandler@ibcg.biotoul.fr">miche.chandler@ibcg.biotoul.fr</a></td>
</tr>
<tr>
<td>Hans-Henrik CHRISTENSEN</td>
<td>Senior manager, New industries Research, Development and Marketing, NOVOZYMES A/S, Simo/mosevej 25, DK-2880 Bagsvaerd, Danemark</td>
<td><a href="mailto:hahk@novozymes.com">hahk@novozymes.com</a></td>
</tr>
<tr>
<td>Jean-Michel CLAVERIE</td>
<td>Information Genomique et Structurale, CNRS, UPR2589, IBSM, 31 chemin Joseph Aiguier, 73402, Marseille, Cedex 20 - France</td>
<td><a href="mailto:jean-michel.claoverie@ips.cnrs-mrs.fr">jean-michel.claoverie@ips.cnrs-mrs.fr</a></td>
</tr>
<tr>
<td>Julian DAVIES</td>
<td>Department of Microbiology and Immunology, University of British Columbia, 300-6174 University Boulevard, Vancouver, BC V6T 1Z3, Canada</td>
<td><a href="mailto:edd@interchange.ubc.ca">edd@interchange.ubc.ca</a></td>
</tr>
<tr>
<td>Christian DESAINTES</td>
<td>Scientific officer, Health and genomics, European commission, Directorate-General for Research - Brussels - Belgium</td>
<td><a href="mailto:christian.desantes@cec.eu.int">christian.desantes@cec.eu.int</a></td>
</tr>
<tr>
<td>Joel DORE</td>
<td>Unité de recherche d'Ecologie et Physiologie du Système Digestif INRA, Domaine de Vilvert 78352 Jouy-en-Josas Cedex - France</td>
<td><a href="mailto:joel.dore@jouy.inra.fr">joel.dore@jouy.inra.fr</a></td>
</tr>
<tr>
<td>Dasko EHRlich</td>
<td>Génétique Microbiologique INRA Domaine de Vilvert 78352 Jouy-en-Josas Cedex - France</td>
<td><a href="mailto:dasko.ehrlich@jouy.inra.fr">dasko.ehrlich@jouy.inra.fr</a></td>
</tr>
<tr>
<td>Catherine ESNOUF</td>
<td>INRA, DS NHISA, 147, rue de l'Université 75007 Paris cedex 07 France</td>
<td><a href="mailto:catherine.esnouf@paris.inra.fr">catherine.esnouf@paris.inra.fr</a></td>
</tr>
<tr>
<td>Jean FIORAMONTI</td>
<td>NeuroGastroenterology &amp; Nutrition Unit INRA 180 Chemin de Tournefeuille, BP 3 F-31931 Toulouse cedex 9 - France</td>
<td>j <a href="mailto:Fioramonti@toulouse.inra.fr">Fioramonti@toulouse.inra.fr</a></td>
</tr>
<tr>
<td>Harry FLINT</td>
<td>The Rowett Research Institute, Greenburn Road, Bucksburn, Aberdeen AB21 9SB, Scotland, UK</td>
<td><a href="mailto:H.Flint@rowett.ac.uk">H.Flint@rowett.ac.uk</a></td>
</tr>
<tr>
<td>Claire FRASER</td>
<td>The Institute for Genomic Research, 9712 Medical Center Drive, Rockville, MD 20850 USA</td>
<td><a href="mailto:claire.fraser@tigr.org">claire.fraser@tigr.org</a></td>
</tr>
<tr>
<td>Claude GAILLARDIN</td>
<td>Microbiologie et Génétique Moléculaire CNRS UMR2585 INRA UMR1238 Institut National Agronomique Paris-Grignon 78850 Thivelval Grignon - France</td>
<td><a href="mailto:claude@grignon.inra.fr">claude@grignon.inra.fr</a></td>
</tr>
<tr>
<td>Philippe GLASER</td>
<td>GIP ANR 1 rue Descartes 75231 Paris Cedex 05 - France</td>
<td><a href="mailto:philippe.glaser@gip-anr.fr">philippe.glaser@gip-anr.fr</a></td>
</tr>
<tr>
<td>Gerhardt GOTTSCHALK</td>
<td>Göttingen Genomics Laboratory, Institute of Microbiology and Genetics, Georg-August-University Göttingen, Grisebachstrasse 6, 37077 Göttingen, Germany</td>
<td><a href="mailto:gopolits@awda.de">gopolits@awda.de</a></td>
</tr>
<tr>
<td>Laurent GUTMAN</td>
<td>Inserm - U 655, Institut Biomédical des Cordeliers 15, rue de l'Ecole de Médecine 75270 Paris cedex 06 - France</td>
<td><a href="mailto:laurent.gutmann@ega-ap-hop-paris.fr">laurent.gutmann@ega-ap-hop-paris.fr</a>; <a href="mailto:gutmann@ccr.jussieu.fr">gutmann@ccr.jussieu.fr</a></td>
</tr>
<tr>
<td>Florence HAIMET</td>
<td>Génétique Microbiologique INRA, Domaine de Vilvert 78352 Jouy-en-Josas Cedex - France</td>
<td><a href="mailto:florence.haimet@jouy.inra.fr">florence.haimet@jouy.inra.fr</a></td>
</tr>
</tbody>
</table>
Egon Bech HANSEN  
Vice President Innovation Bioscience  
DANISCO A/S  
Langebrogade 1  
DK-1001 Copenhagen K - Denmark  
egon.bech.hansen@danisco.com

Masahira HATTORI  
Riken Genomics Science Center, RIKEN Yokohama Institute, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa, 223-0045, Japan  
hattori@gsd.riken.go.jp

Tetsuya HAYASHI  
Department of Microbiology, Miyazaki Medical College, 5300 Kiyotake, Miyazaki 895-1692, Japan  
hayashi@post.miyazaki-med.ac.jp

Brian JONES  
Department of Microbiology & Alimentary Pharmabiotic Centre  
University College Cork, College Road  
Cork - Ireland  
B.Jones@ucc.ie

Matthew KANE  
Program Director  
Division of Molecular and Cellular Biosciences  
National Science Foundation  
4201 Wilson Blvd  
Arlington, VA 22230 - USA  
rmkane@nsf.gov

Marion KARRASCH-BOTT  
ERA-NET PathoGenoMics - Joint Secretariat  
Forschungszentrum Juelich  
Project Management Juelich, Division BIO D-52425 Juelich  
m.karrasch@fz-juelich.de

Michiel KLEEREBEZEM  
Wageningen Centre for Food Sciences, NIZO Food Research, Kemhewmeweg 2, PO Box 20, 6710.BA Ede, The Netherlands  
Michiel.Kleerebezem@nizo.nl

Frank KUNST  
Directeur de Pasteur Genopole Ile-de-France  
Institut Pasteur  
Unité de Génomique des Microorganismes Pathogènes  
28, rue du Dr Roux, 75724 Paris Cedex 15 - France  
fkunst@pasteur.fr

Denis LE PASLIER  
Genoscope - CNS, 2 rue Gaston Cremon, CP 5706, 91057 Evry Cedex - France

Marion LECLERC  
Unité de recherche d'Écologie et Physiologie du Système Digestif  
INRA Domaine de Villevert  
78352 Jouy-en-Josas Cedex - France  
Marion.Leclerc@jouy.inra.fr

Xavier LEVERVE  
Direction Scientifique  
Nutrition Humaine et Sécurité des Aliments  
Institut National de la Recherche Agronomique (INRA)  
147, Rue de l'Université, 75007 Paris - France  
xavier.leverve@paris.inra.fr

Roderick I. MACKIE  
Department of Animal Sciences, University of Illinois at Urbana-Champaign  
r-mackie@uiuc.edu

Dennis MANGAN  
National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, 20892-2190 - USA

Julian R. MARCHESI  
Department of Microbiology & Alimentary Pharmabiotic Centre, University College Cork, College Road, Cork - Ireland  
j.marchesi@ucc.ie

Philippe MARLIERE  
Genoscope - CNS, 2 rue Gaston Cremon, CP 5706, 91057 Evry Cedex - France  
phm@genoscope.cns.fr

Pierre MONSAN  
Molecular Enzyme Engineering Team, CNRS INRA INSA  
135, avenue de Rangueil  
31077 Toulouse Cedex 4 - France  
Pierre.Monsan@insa-toulouse.fr

Mark MORRISON  
The Ohio State University,  
110E ASL,  
2029 Fyffe Court,  
Columbus, OH 43210-1095 - USA  
morrison.234@osu.edu

Renaud NALIN  
C.E.O., LIBRAGEN  
Bat.Canal Biotech I, 3, rue des Satellites  
31400 Toulouse - France  
contact@libragen.com

Elisabeth NAVARRO  
Ecologie Microbenne UMR CNRS 5557, Bat. Gregor MENDEL  
Université Claude-Bernard Lyon1  
43 bld du 11 November 1918  
69622 Villeurbanne cedex France  
navarro@univ-lyon1.fr

Karen NELSON  
The Institute for Genomic Research, 9712 Medical Center Drive, Rockville, MD 20850 - USA  
kenelson@tigr.org

Naotake OGASAWARA  
Nara Institute of Science and Technology (NAIST), 8916-5 Takayama, Ikoma, Nara 630-0101, Japan  
nogasawa@mba.sphere.ne.jp

Julian PARKHILL  
The Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SA, UK  
parkhill@sanger.ac.uk

Eric PELLETIER  
Genoscope - CNS, 2 rue Gaston Cremon, CP 5706, 91057 Evry Cedex - France  
ericp@genoscope.cns.fr

Remy PERRIN  
SOREDAB, La Tremblaye,  
78 125 La Boissière Ecole - France  
remi.perrin@soredab.com

Jane PETERSON  
National Human Research Institute, 31 Center Drive, Rockville, MD 20892 - USA  
petersoj@exchange.nih.gov

Francis QUETIER  
GIP ANR  
1 rue Descartes  
75231 Paris Cedex 05 - France  
francis.quetier@gip-anr.fr
David RELMAN  
Associate Professor of Microbiology & Immunology, and of Medicine  
Stanford University,  
Chief, Infectious Diseases Section  
VA Palo Alto Health Care System  
Building 101, Room B4-185  
3801 Miranda Avenue  
Palo Alto, CA 94304 - USA  
reman@stanford.edu

Eddy M. RUBIN  
Department of Energy (DOE) Joint Genome Institute, 2800 Mitchell Drive,  
Walnut Creek, CA 94598 - USA  
emrubin@lbl.gov

Vincent SCHACHTER  
Genoscope - CNS , 2 rue Gaston Cremieux,  
CP 5706, 91057 Evry Cedex - France  
vs@genoscope.cns.fr

Abdelanii SGHIR  
Genoscope - CNS , 2 rue Gaston Cremieux,  
CP 5706, 91057 Evry Cedex - France  
sghir@genoscope.cns.fr

Pascal SIMONET  
Ecologie Microbienne (Microbial Ecology)  
UMR CNRS 5557, Université Claude Bernard, Lyon 1,  
Domaine Scientifique de La Doua, Bat.G. Mendel  
43 bd du 11 November 1918  
69622 Villeurbanne Cedex - France  
simonet@biomserv.univ-lyon1.fr

Mahavir SINGH  
GBF (German Research Centre for Biotechnology) Mascheroder Weg 1, D-38124 Braunschweig, Germany  
mcis@gbf.de

Lothar STEIDLER  
Alimentary Pharmabiotic Centre,BioSciences Building, University College Cork, Ireland  
l.steidler@ucc.ie

Rick STEVENS  
The University of Chicago and Argonne National Laboratory  
9700 South Cass Avenue, Building 221  
Argonne, IL 60439 - USA  
stevens@cs.uchicago.edu

Andreas TAUCH  
Dept. of Genetics, Faculty of Biology, University of Bielefeld P.O.Box 100131, D-33501 Bielefeld - Germany  
Andreas.Tauch@Genetik.Uni-Bielefeld.DE

Kenneth TIMMIS  
Professor and Head Division of Microbiology GBF - National Research Centre for Biotechnology Mascheroder Weg 1D-38124 Braunschweig - Germany  
kti@gbf.de

Christian VALIN  
INRA  
147, rue de l’Université  
75338 Paris cedex 07 - France  
valin@clermont.inra.fr

Elaine VAUGHAN  
Assistant Professor Wageningen University Laboratory of Microbiology UNILEVER R&D  
The Netherlands  
Elaine.Vaughan@wur.nl

Stanislas VEILLET  
DANONE VITAOPE  
Route Départementale 126  
91767 Palaiseau Cedex France  
stanislas.veillet@danone.com

Gaby VERONESE  
INSA, Equipe Ingénierie Enzymatique Moléculaire  
Département de Génie Biochimique et Alimentaire  
135 avenue de Rangueil  
31077 Toulouse cedex 4, France  
veronese@insa-toulouse.fr

Ulrich Vogel  
Institut fur Molekulare Infektionsbiologie, University of Wurzburg, Josef-Schneider-Straße 2, D-97080 Wurzburg, Germany  
uvogel@hygiene.uni-wuerzburg.de

William WADE  
Department of Microbiol., Floor 28, Guy's Tower, Guy's Hospital, London SE1 9RT, UK  
william.wade@kcl.ac.uk

Jing WANG  
Assistant Director & Associate Prof.  
Beijing Institute of Genomics of the Chinese Academy of Sciences, B-6  
Beijing Airport Industrial Zone, Beijing, 101300 China  
wangjing@genomics.org.cn

George WEINSTECK  
Human Genome Sequencing Center, Baylor College of Medicine, One  
Baylor Plaza, Alkek N1519, Houston, TX 77030 - USA  
gwstock@bcm.tmc.edu

Jean WEISSENBACH  
Directeur, Genoscope - CNS , 2 rue Gaston Cremieux,  
CP 5706, 91057 Evry Cedex - France  
jsbach@genoscope.cns.fr

Liping ZHAO  
Associate Dean, Shanghai,Institute for Systems Biology, Shanghai Jiao Tong University, College of Life Science and Biotechnology, Lab of Molecular Microbial Ecology & Ecogenomics, 800 Dong Chuan Road, Shanghai 200240, P.R. China  
pzhao@siu.edu.cn

MaryJo ZIDWICK  
CARGILL, Biotechnology Development Center P.O. Box 5702 Minneapolis, Minnesota 55440 USA  
MaryJo.Zidwick@cargill.com