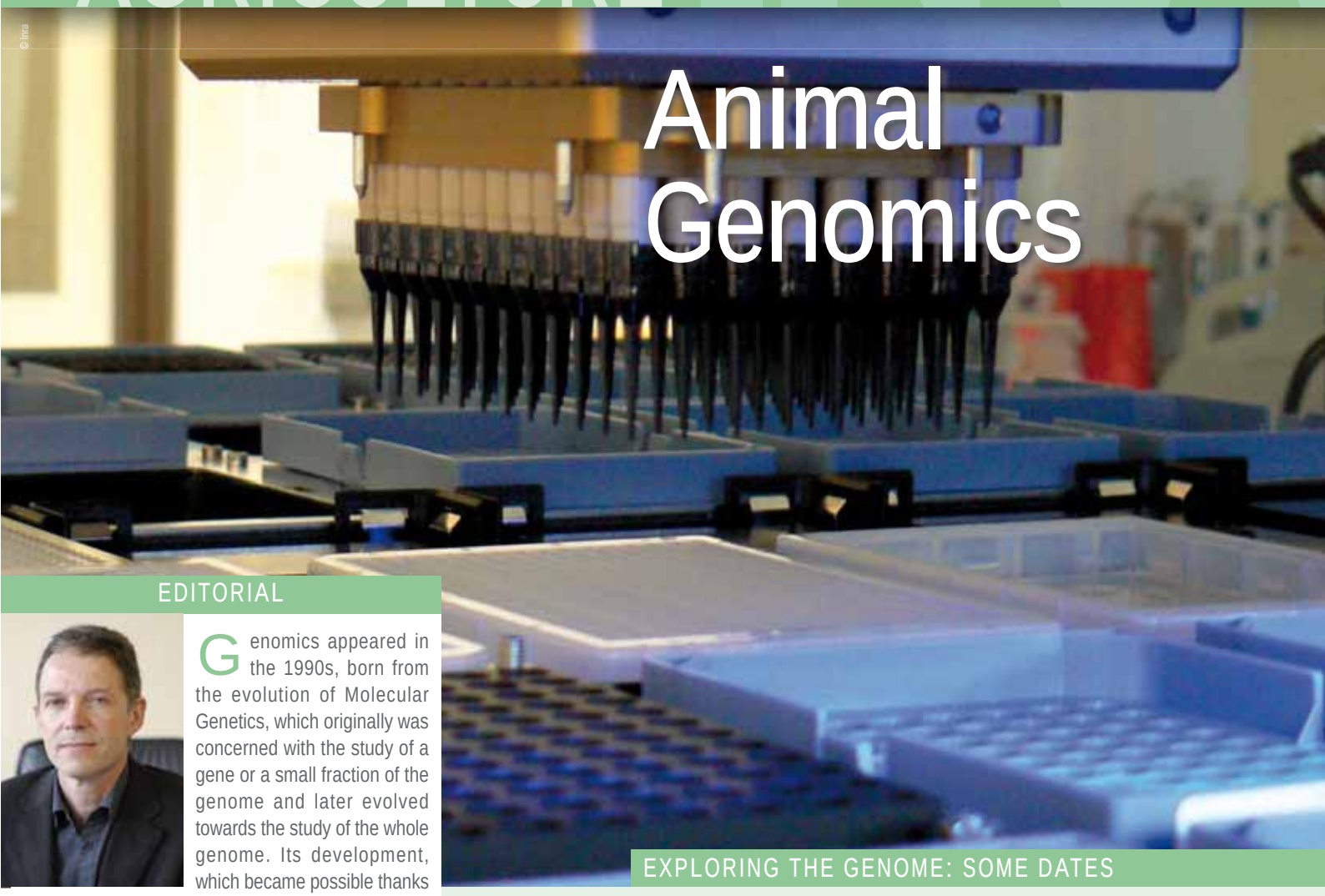
FEBRUARY 2009

FOOD AND NUTRITION
ENVIRONMENT
AGRICULTURE



Animal Genomics

EDITORIAL

Genomics appeared in the 1990s, born from the evolution of Molecular Genetics, which originally was concerned with the study of a gene or a small fraction of the genome and later evolved towards the study of the whole genome. Its development, which became possible thanks to major technological innovations, has renewed the scientific questioning of Biology, with the hopes of learning more about the complex functioning of living organisms.

INRA rapidly invested in these new approaches, convinced of their importance to answer the challenges met by farming, in relation to the increased world-wide demand for healthy, high-quality food, the necessity of sustainable economics and environments of breeding systems and the need to adapt to global changes. INRA has thus mobilised its competencies in Animal Biology, Bioinformatics and Applied Mathematics to generate and make the most of new data in Genomics. Alone or with partners in international consortia, INRA contributes to increasing our knowledge of how living organisms function. In partnership with the Cirad, INRA has become an ally of organisations for livestock production in order to conceive innovations together, which are necessary to answer these challenges.

Scientific Director Animals
and Animal Products, INRA

EXPLORING THE GENOME: SOME DATES

1953: discovery of the **molecular structure of DNA**

1961-1965: decoding of the **genetic code**

1977: first method developed for DNA **sequencing**

1980: the principle of **genetic mapping** by anonymous molecular markers

1987: first **"automatic" DNA sequencing** machine developed

1990: publication of the BLAST algorithm for the **comparison of DNA sequences**

Sequencing of the **human genome**:
- First map of genetic markers of the human genome in 1987
- Birth of the sequencing project in 1988 and the first version in 2001
- The genome sequence was considered as complete in 2004

Sequencing of the **genome of *Arabidopsis thaliana***:
- Launching of the project in 1992
- Sequence complete in 2000

Sequencing of **farm animal genomes**:
- The construction of maps of genetic markers for cattle, pigs and chicken began in the 1990s
- Transcriptomic analysis began in the year 2000
- **First version** of the sequence of the **chicken genome was obtained in 2004** (sequencing began in 2002), **that of cattle in 2006, the horse in 2007 and the pig in 2009.**

AN INTERVIEW WITH SERGE PARAN

PRESIDENT OF THE NATIONAL UNION OF ARTIFICIAL ANIMAL INSEMINATION COOPERATIVES (UNCEIA)

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What are the expectations of the National Union of Artificial Animal Insemination Cooperatives towards genomic research?

S.P.: Selection of the bovine species has shown its efficacy, however, its cost is high since it is mainly based on progeny testing in a species with a long generation interval and a low female reproductive potential.

Simplifying and improving the efficacy of this mission is therefore an important stake for both selection professionals and breeders. With this in mind, UNCEIA and all selection professionals have invested along with INRA in genomic research. First, this concerned the search for QTL implicated in the quality of bovine reproducing animals followed by a first MAS programme with microsatellite markers, then with SNP microarrays and second generation MAS arriving in October 2008.

The partnership between the industry and public research has been exemplary and has maintained France as a leading country in bovine selection.

How is the industry organising itself keeping in mind Animal Genomics innovations?

S.P.: The importance of Genomics is not limited to selection therefore since a big effort is necessary, the organisations for livestock production decided to consolidate their partnerships with research by creating Apis-Gène. This interprofessional SAS, a member of the GIS AGENAE, is aimed at participating in genomic research and has the capacity to finance, along with the National Research Agency (ANR), finalised research projects in reproduction, selection, product quality, health and animal welfare. Many important research projects have thus been made possible, such as Qualvigène, FertiVLHP, Phenofinlait, Cartofine, Amasgene and many others, improving our knowledge of the genetic determinism of important physiological functions implicated in animal production systems.

Even though research has already led to concrete results in selection, for the rest we are only halfway along; the following phase will be decisive for us to obtain the best results from our effort. But this is worth it and is why organisations for livestock production renewed Apis-Gène, extending partnerships with INRA within the framework of the GIS AGENAE for another five years.

"Knowledge of Genomes for Tomorrow's Animal Breeding"

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Animal genomics is one of the main axes of research in the field of Animal Sciences due to its perspectives in genetic improvement but also an improved adequacy between animals and husbandry methods. It allows acquiring generic knowledge on the structure and functioning of genomes, obtained from molecular data issued from more and more performing technologies. As a complement to genomic data, the acquisition of phenotypic data as measures of various traits at different stages of their biological development, provides extremely fine and precise characterisation of the animals studied in different environments.

The combined use of these different types of both genomic and phenotypic data, improves our understanding of the complex biological interactions and regulations that control animal characteristics and variability. We thus dispose of a solid base for treating questions of finalised research, built along with our partners, to answer the new demands imposed to husbandry.

RESEARCH TOOLS AT INRA

The technological and methodological investments necessary to obtain genomic data have led INRA to build specialised platforms organised as networks such as the GADIE Biological Resource Centre (DNA databanks, transcriptomics), Labogena or Genotoul (sequencing and genotyping) and the bioinformatics platform SIGENAE, which are part of the national organisation of genomic structures and integrated in European research.

The management and interpretation of diverse experimental data produced in large numbers necessitates competencies in Biology, Computer Sciences, Bioinformatics and Applied Mathematics. The grouping together of such competencies acts through important programmes, benefiting from the ANR (Genanimal) and professional organisations (AGENAE) on the national level or from European or international support.

A RESEARCH PARTNERSHIP: THE SCIENTIFIC INTEREST GROUP AGENAE

Since 2002, AGENAE has been federating INRA and CIRAD research teams and four inter-professional partners focussing on cattle and small ruminant species (ApisGene), pigs (Bioporc), poultry (Agenavi) and fish (CIPA). In 2009, the adhesion of the National Haras and Ifremer extended this activity to horses and shellfish. Its activities are aimed at improving knowledge of the genomes of livestock and how they function in order to improve and evolve husbandry in the current and future socio-economic context.

AGENAE, along with the ANR, participates in building project calls for the financing of research programmes. This original structure has led to the rapid development of applications and innovations issued from genomics in livestock production.

http://www.agenae.fr/programme_agenae/

THE EUROPEAN EXCELLENCE NETWORK EADGENE

The European Network of Excellence EADGENE (European Animal Disease Genomics Network) was created in 2004 for five years within the framework of the improvement of Animal Health, Food Quality and Safety. Its objective is to coordinate and orient pluridisciplinary research in genomics of host-pathogen interactions. Fifteen European research institutes are involved in EADGENE, coordinated by INRA. Companies from small and medium sized enterprises, grouped together as a "club of interest", form a network that favours technological transfer by an improved adequacy between the needs expressed and the research developed. The research developed in Population Genetics, Structural and Functional Genomics are relative to the mechanisms of resistance and defence of different pathologies: mastitis (ruminants), salmonellosis (pigs, poultry), infections due to *Escherichia coli* (cattle), viral diseases (fish).

http://www.eadgene.org/

ADVANCES IN GENOMICS

In farm animal species, genomics began in the 1990s with the elaboration of maps of genetic markers spread throughout the whole genome, libraries of DNA fragments of different sizes allowing access to different regions of the genome and comparative mapping of species. Since the beginning of the 2000s, the evolution of sequencing technologies and bioinformatics methods provided sequence data of the expressed fraction of the genome (or transcriptome), then rapidly, the sequencing of complete genomes of farm animals. INRA has contributed much to all these advances, generally within the framework of international consortia.

Although incomplete, the sequence of complete genomes, available to the international community on the internet, leads to new possibilities for the understanding of living organisms. Among the potential applications, the following can be highlighted : sequence comparison of species and notably its contribution to the knowledge of species evolution; the identification of DNA polymorphisms between different individuals of the same species and the rapid genotyping of many animals, made possible by new high-throughput genotyping tools like SNP microarrays; the analysis of total genome expression using transcriptomic arrays and new protein analysis methods leading to the proteome; and the analysis of the transcripted non-coding genome and the discovery of new methods of regulation of gene expression (small RNA, methylation, epigenetics).

THE CONTRIBUTION OF FUNCTIONAL GENOMICS

The development of genomics technologies has led to new questions concerning the functioning of living organisms. It has become possible to obtain at one time information on the level of expression of all genes expressed in a cell, a tissue, in a defined biological state by transcriptomic or proteomic analysis. This has allowed exploring the relations between these different molecules and their modifications during the development of the organisms, or under the effect of external factors like nutrition, husbandry conditions, and sanitary conditions all in relation with the animal's characteristics.

This is a new approach to Biology, leaving the "reductionist" era and entering that of Biological Systems, allowing the identification of mechanisms of responses of organisms to various situations as a whole. All biological functions are concerned (nutrition, reproduction, development, immunity, behaviour, etc) and the study of complex traits has become possible.

There are many applications of this new knowledge for livestock production, especially within today's context of important changes. Livestock production methods will be able to be better adapted to the physiology of animals, as a function of the defined production objectives. The consequences of the different choices will be better controlled.

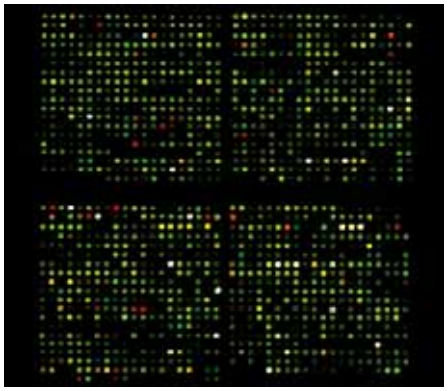
GENOMIC SELECTION

Genomic Selection is a revolution in Animal Genetics. It allows selecting breeding animals on the basis of the genetic value predicted with genetic markers spread all over the genome. This approach is possible thanks to the availability of 50000 to 60000 SNP microarrays for an increasing number of species.

Genomic selection relies on a "reference" population that has been genotyped and phenotyped, allowing the establishment of equations that predict a genetic value and that are applied to the rest of the population. The larger the reference population, the better are the predicted values.

This selection considerably makes the selection schemes easier by reducing the need for performance recording and by suppressing the need for pedigree information. Genetic progress may be acquired more rapidly since the generation interval is shortened. In addition, selection intensity may be high if the cost of genotyping is sufficiently low to allow an important screening of the population. This selection method is very advanced in dairy cattle, with enough precision to question the necessity of progeny testing. Similar efforts are currently being led in other species.

Genomic selection will deeply transform the breeder's profession in the near future. It will lead to selection of new traits for a more sustainable breeding in both northern and southern countries.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GLOSSARY

Coding DNA: a portion of a DNA sequence that can be translated to protein

Genotyping: ccharacterisation of variants of a DNA sequence belonging to one individual

(genetic) Marker: polymorphous region (different between individuals) of a DNA molecule; they are aligned forming a map of genetic markers

Microsatellite: a very small portion of DNA repeated differently in different individuals

Phenotype: an observed or measured value of traits in an individual

Microarray (DNA): a glass slide containing on its surface millions of small DNA fragments used for different analyses (microarrays of transcriptomes, SNP)

QTL (quantitative trait loci): a region of a genome whose polymorphism explains a large part of the variability of a measured trait

MAS: Marker Assisted Selection

Proteome: the set of proteins present in a tissue

SNP (Single Nucleotide Polymorphism): polymorphism of one single nucleotide at a specific position of a DNA sequence

Transcriptome: the set of genes expressed at the RNA level present in a tissue

FERTILITY OF HIGH-PRODUCING DAIRY COWS

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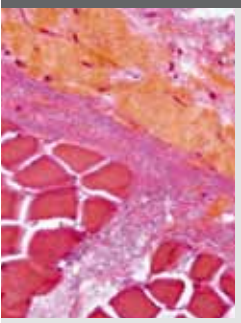
Selection of dairy cattle for the past approximately thirty years has led to an important and sustained increase of milk production along with a regular decrease of female fertility. Several research programmes have studied the genetic and physiological determinism of this decrease in fertility. One of them has for example, allowed the identification of several QTL responsible for this phenomenon in three main French dairy breeds. The use of high-throughput genotyping has recently allowed the important discovery of their precise positions in the bovine genome, which will allow the identification of genes responsible for the quantitative trait variation. In addition, a detailed phenotyping, associated to genetic information, will permit the study of the physiological mechanisms causing this reduced fertility. Research has also allowed the identification of markers for oocyte quality. All these studies should help eliminate the alleles responsible for this reduced fertility from herds and /or adapt the husbandry methods to the genotypes.

THE QUALITY OF MEAT PRODUCTS



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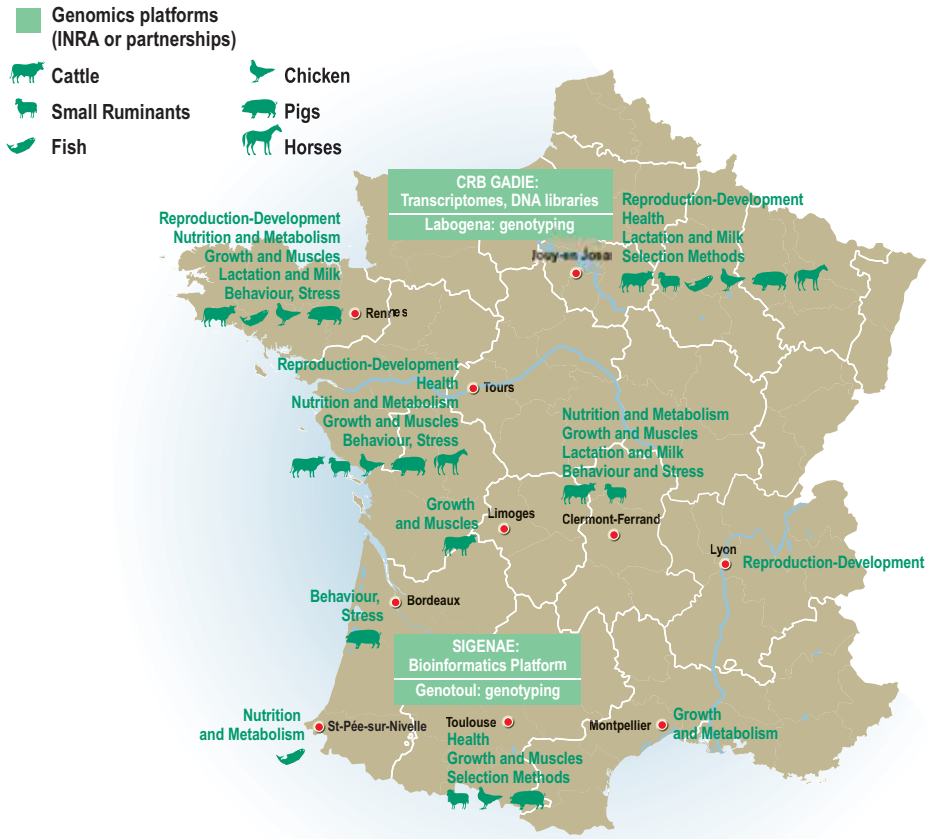
The improvement of animal product quality remains an important preoccupation in animal livestock production and the recent results obtained give good reasons to think that Genomics may be able to make an important contribution. In sheep, the identification of the causal mutation and the original mechanisms of action responsible for high muscle development, associated with meat quality in the Belgian Texel breed was a major discovery in recent years. Promising results have already been obtained for the genetic determinism of tenderness and other sensorial qualities of bovine meat. In the chicken, a gene that controls meat colour was recently identified. There is hope as well that by using genomics, new elements will lead to an alternative to castration of males for the production of pig meat with good organoleptic qualities.

ANIMAL GENOMICS AT INRA



SOME ANIMAL GENOMICS PROGRAMMES

National (supported by the Genanimal ANR) – Led by INRA with academic partners

VacGenDC – 2006: Genetic profile of dendritic cells in response to new vaccine candidates : application to an emerging disease of ruminants (ovine bluetongue disease).

Arcange – 2006: Development of bioinformatics tools for the comparative analysis of genomes.

ChickRH – 2006: Irradiation mapping of the chicken: dense mapping of SNP and localisation of Expressed Sequence Tags (EST) that are absent from the genome sequence.

Oscile – 2008: Somatic cell-oocyte interactions, a study of comparative genomics in vertebrates (trout, cattle, mice, African clawed frogs).

National (supported by the Genanimal ANR and AGENAE) – INRA, professional and academic partnerships.

Qualvigene – 2002 – Qualvigena – 2005 – Qualvigenb – 2006: detection and validation of the genes implicated in bovine meat quality of the three main meat breeds in France.

Mammifert – 2005: use of congenic recombinant mice for rapid positional cloning of QTL in mammals: application to fertility QTL in mice, domestic cattle and man.

Fertilité 1 – 2005 – Fertilité 2 – 2006: Genetic determinism and metabolic studies of fertility problems of high-producing dairy cows.

Flavores – 2007: Study of defence mechanisms and genes implicated in resistance to *Flavobacterium psychrophilim*, a bacteria responsible for high mortalities in salmon farms.

DéLiSus – 2007: Study of the haplotypic variability of the porcine genome allowing the detailed analysis of genetic diversity of the main French breeds.

Amasgen – 2008: Methodological approaches and applications in genomic selection of dairy cattle.

European

SABRE (2006-2010): an integrated project whose objective is the use of the progress of genetic methods for the development of sustainable livestock production. This includes 33 partners from 14 countries. INRA is present or is the leader in 8 of the 10 work packages.

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