Health and food: Genomics science towards the development of new drugs and stress tolerant plants

6th German-Brazilian dialogue on science, research and innovation
FAPESP, November, 8-9th 2017

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HEALTH

The dilemma of pharmaceutic industry in developing new drugs
Industry R&D return on investment (ROI) as calculated in Deloitte's innovation report 2015.
The costs of developing new drugs are estimated at USD 2.6 billion, more than twice the value in 2013.


Dickson & Gagnon (2014) Nature Reviews Drug Discovery
The increase in costs is because most drug candidates fail for lack of efficacy

- **2007-2010**
  - Phase II - 51%
  - Phase III - 66%
- **2011-2012**
  - Phase II - 59%
  - Phase III - 52%
- **2013-2015**
  - Phase II - 48%
  - Phase III - 55%

Lack of efficacy

- Biology is poorly understood
- Target was not properly validated

- These failures are expensive
- These failures are duplicated in multiple companies
Most studies for target validation is not reproducible

Work at Bayer found that **out of 67** published target-validation studies, **only 20-25% were reproducible**

- Urgent need for good quality tools to help enable reproducible science

Prinz et al. (2011) Nature Reviews Drug Discovery
FOOD

The drought and high temperature stress imposed by climate changes constitute a significant threat to food production
Global food consumption and its sources

- The main sources of energy for human are carbohydrates from cereals, fats from leguminous plants and animal, milk and eggs, fruits and vegetables, meat and fish.

- Carbohydrates, fats, milk, eggs and meat, that together account for 80-90% of the energy consumed by human, are directly or indirectly derived from 5 crops: rice, maize, soybean, wheat, and sugarcane.

- To meet the energy needs of a population estimated at 9 billion by 2050, it will be necessary to increase the productivity of these five crops by 50-60%.

An extreme drought (and heat) in the 2012/13 crop imposed a loss of 40 Million Tons of maize. This is equivalent to the average of Brazilian production in the period 2005-2010 (49 Mt).
Genome science will have a real impact on all our lives -- and even more, on the lives of our children. It will revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases.

...In fact, it is now conceivable that our children's children will know the term cancer only as a constellation of stars.

...Researchers in a few years will have trouble imagining how we studied human biology without the genome sequence in front of us.

June 26, 2000
How can -omics promote ...

Health
- Finding disease-linked gene variants
- Understanding mechanisms of disease
- New drug targets
- Genotyping – tailoring cures to patients
- Molecular diagnosis
- Opening up unexplored areas of human biology
- Genome editing

Food production
- Finding disease-linked gene variants
- Understanding mechanisms of disease and stress response
- New traits associated genes
- Genotyping – tailoring custom varieties
- Molecular diagnosis
- Opening up unexplored areas of plant biology
- Genome editing
Secrecy imposed by early stage IP protection delay the process of Drug Discovery

The Structural Genomics Consortium (SGC) open innovation model to accelerate DDD

- The GSC was founded in late 2003 with funding from the Wellcome Trust and GlaxoSmithKline to establish a Public Open Innovation Consortium
- It commenced operations in June 2004 at the Universities of Oxford and Toronto and has since expanded its PPP network
- In September 2017 the SGC network comprises +280 researchers in Oxford, Toronto, Stockholm, Campinas, Chapel Hill and Frankfurt
- The GSC is currently funded by large pharmaceutical companies and governmental agencies
- **Open Science Policy**: Promptly placing results, reagents and know-how in the public domain. SGC scientists don’t file patents
SGC genome-scale work on Human Kinases

Kinases are potential targets for DD as it is involved in almost all cellular metabolism and is linked to diseases like cancer, pain, inflammation, etc.

Currently there are 42 Kinase targeted medicines in the market to treat these diseases

38 human kinase structures pre-SGC
80 human kinases solved by SGC
~20 kinase probes
The SGC-UNICAMP platform: From the gene to the probe through genomics and medicinal chemistry
The SGC-UNICAMP platform: In less than 2 years our scientists developed the first probe for Kinase target.

2nd series of AAK1 inhibitors were potent, cell-permeable and did not show toxic effects to cells.

Approved SGC probe!

![Cell Cycle Analysis](chart1.png)

![NanoBRET AAK1](chart2.png)

SGC-AAK1-1
FOOD
The Genomics for Climate Change Research Center

From the gene to the trait

Academic Partners
- University of Campinas
- University of Nottingham
- VIB/Ghent University
- University of Delaware
- University of Western Australia
- Technical University of Madrid (UPM)

Industry Partners
- Biotechnology Startup: Pangeia Biotech

Improved cultivars

Embrapa Centers
- Agricultural Informatics
- Agroenergy
- Biotechnology & Genetic Resources
- Cerrados
- Cotton
- Instrumentation
- Maize and Sorghum
- Soybean
- Wheat
Unlocking the bacterial and fungal communities assemblages of sugarcane microbiome

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sample type</th>
<th>Compartment</th>
<th>Developmental stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td>Leaves</td>
<td>Exophytic</td>
<td>4th month</td>
</tr>
<tr>
<td></td>
<td>Upper stalk</td>
<td>Exophytic</td>
<td>6th month</td>
</tr>
<tr>
<td></td>
<td>Medium stalk</td>
<td>Endophytic</td>
<td>8th month</td>
</tr>
<tr>
<td></td>
<td>Bottom stalk</td>
<td>Endophytic</td>
<td>10th month</td>
</tr>
<tr>
<td></td>
<td>Young Shoot</td>
<td>Endophytic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Root</td>
<td>Exophytic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bulk Soil</td>
<td>Endophytic</td>
<td></td>
</tr>
</tbody>
</table>

Bacterial community (16S – V4 region)

Fungal community (ITS – ITS2 region)

HiSeq 2500, 250bp paired end reads, average of 1MM reads per sample

(i) Sugarcane ratoon at 4th month after budding
(ii and iii) Stalks
(iv) Stalk before (left) and after (right) microbiome sampling
(v and vi) Leaf exophytic microbiome sampling
(vii) Ratoon excavation
(viii) Exophytic root microbiome sampling from soil
(ix and x) Roots during sampling procedure
16S and ITS massive amplicons sequencing revealed ~22K bacteria and 10K fungi groups inhabiting the sugarcane

- A significant proportion of the microbial diversity is shared among samples
- But plant organs select their most preferable microbes probably through functional enrichment
- Soil serves as reservoir for the assemblage of plant organ microbiota
Impact of an abundant-based synthetic community in plant growth

**Proof of concept:** Synthetic community made with 20 highly abundant bacteria in sugarcane organs

![Graph showing relative abundance and weight changes](image)

**Proof of concept:** Synthetic community made with 20 highly abundant bacteria in sugarcane organs

![Images of plant growth](image)
Highly abundant bacterial are robust colonizers

Microbiome mapping revealed that the synthetic community made with highly abundant sugarcane bacteria inoculated in maize plants displaced the natural maize microbiota, efficiently colonize the plant organs, and stimulate the root system and plant growth.

<table>
<thead>
<tr>
<th>Synthetic community OTUs</th>
<th>Uninoculated</th>
<th>Inoculated</th>
<th>Relative abundance in row</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Root</td>
<td>Stem</td>
<td>Leaf</td>
</tr>
<tr>
<td></td>
<td>19. Dyella</td>
<td>20. u_Streptomycetaceae</td>
<td>21. ...</td>
</tr>
</tbody>
</table>

(b) Relative abundance (%)

- **Uninoculated plants**
- **Inoculated plans**

![Heatmap of bacterial abundance in maize plants](image-url)
Robust colonizers are enriched in genes encoding specific functions

- The complete genome sequences of the synthetic community revealed 26 bacteria;
- Robust colonizers share a set of enriched functions;
- Some of the specific functions are absent in non-robust colonizers;
- Genes related to carbohydrate metabolism, energy production and secondary metabolites are among the top categories that are enriched in the robust colonizers;
Unlocking the mechanism of extreme drought stress tolerance through genomics of Velloziaceae species

Velloziaceae species growing in exposed rocks and shallow patches of soil in Brazilian campos rupestres (rupestrian grasslands) (A,B,C). Example of a desiccated Vellozia nivea (ressurection) after four months without rain and the same plant six days after rain, respectively (D). Vellozia intermedia (ever green) after four months without rain and the same plant six days after rain, respectively (E-F).
Our goal: Cross-talk between biomedical and plant sciences to boost innovation for new medicine and food production in a more sustainable way

SGC + GCCRC = Knowledge synergism in using genomics tools