6th Plant Genomics & Gene Editing Congress: Europe
14-15 May 2018, Rotterdam, The Netherlands

# Genome Editing In Agriculture … An Industry Perspective On Requirements For Robust Outcomes Beyond Low Hanging Fruits

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KWS


# About KWS Saat SE

# KWS at a glance
## Company highlights & financials

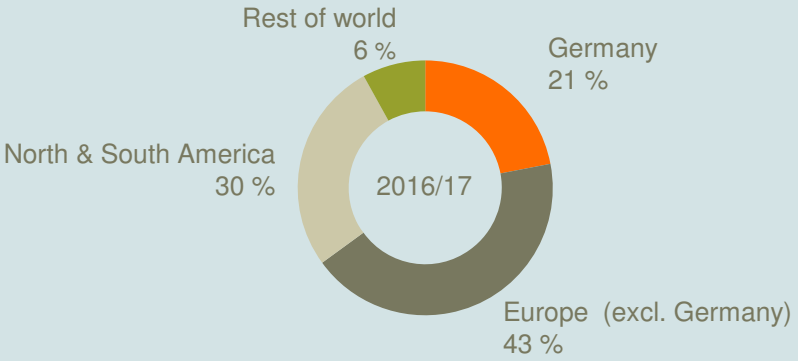
### Company highlights

- World market leader in high value agricultural niche crops and strong position in global corn market
- Sustainable business model with strong fundamental pillars (global demand for food and feed)
- Strategy and management with long-term orientation, enabled by family shareholders

### Key financials of the KWS Group

| in € million | 2016/2017 | 2015/2016 | + / – |
|---|---|---|---|
| Net sales | 1,075.2 | 1,036.8 | +3,7% |
| R&D expenses | 190.3 | 182.4 | +4.3% |
| EBIT | 131.6 | 112.8 | +16.7% |
| EBIT margin (%) | 12.2 | 10.9 | +11.9% |

### Net sales by region



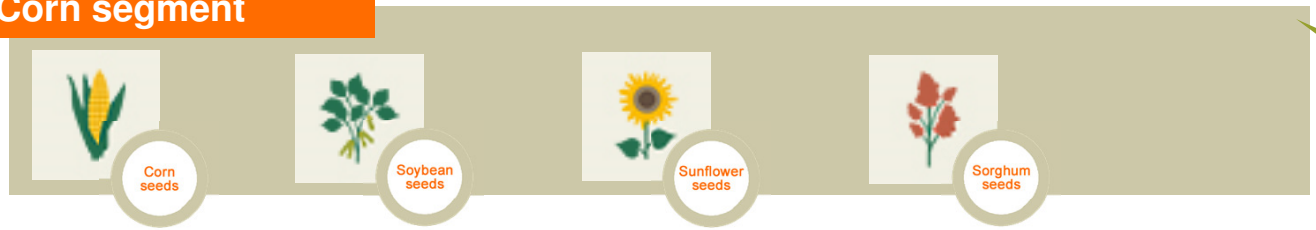

### 10-year sales development

# Expert in seeds
## Comprehensive portfolio of agricultural crops

### Sugarbeet segment


Marketing approvals in 15/16 for new varieties: **174**

### Corn segment




Marketing approvals in 15/16 for new varieties: **153**

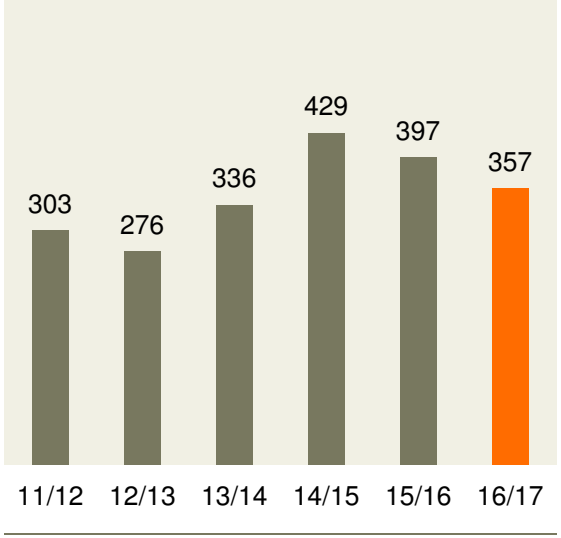
### Cereals segment


Marketing approvals in 15/16 for new varieties: **70**

**Specialized in developing, producing and distributing high-quality seeds for agriculture**

# Key to success
## Efficient variety development

### Marketing approvals for new varieties



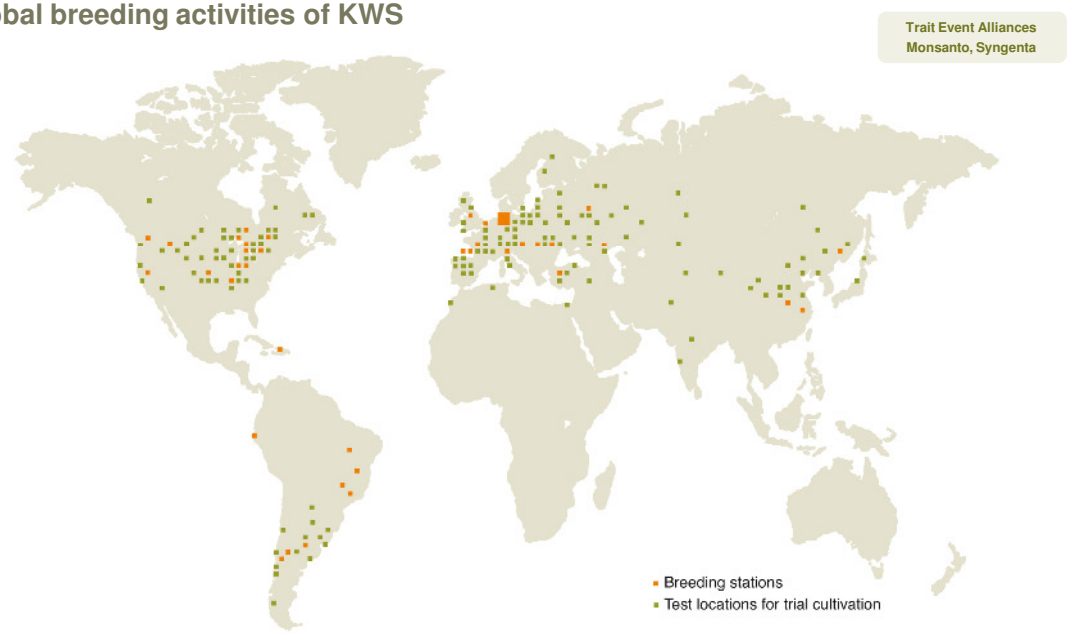

**R&D expenditure:**
**17.7% of net sales**

**Ø yield progress:**
**1% to 2% per year**

### Plant breeding requires cutting edge technology

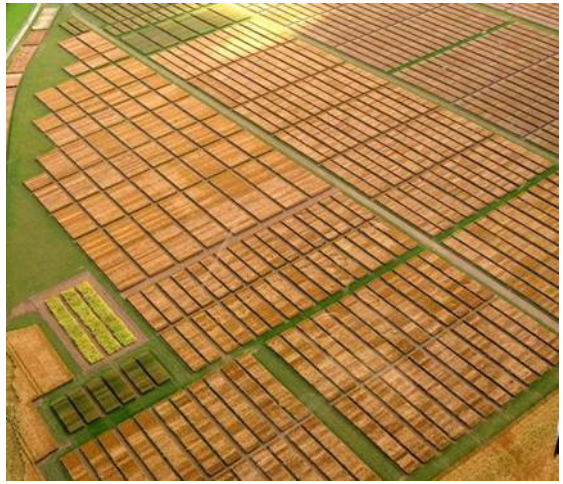
- Phenotyping
- Genomics & Markers
- Cell & Tissue Culture
- GM & GE Traits
- Genetic Variation
- Breeding Competence
- New Breeding Technologies
- Bioinformatics

### Global breeding activities of KWS



# Need for continuous innovation
## Essential business processes

**Continued improvement of Yield & Quality Characteristics**



**Reliable Seed Quality**

**Top Class Personal Consulting**

Year on Year Innovation
Competitive Product Performance

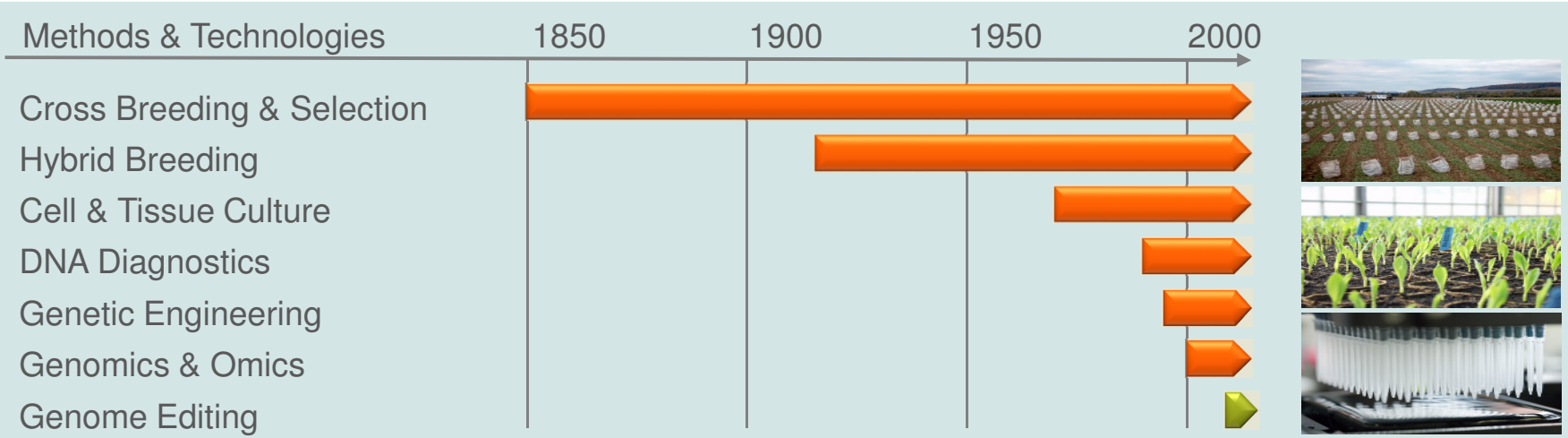
**Farmers´ trust**

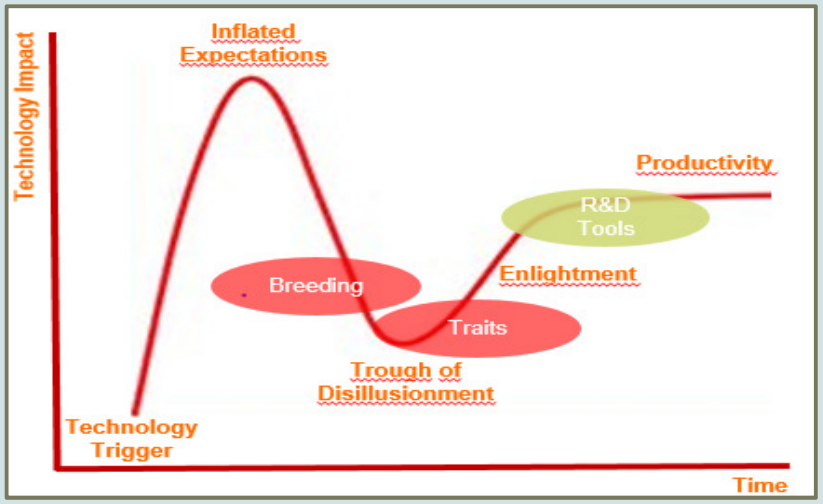
# Innovations in Plant Breeding

## Targeted Genome Editing

## From Opportunity to Reality

# Key Innovations in Plant Breeding
## From technology trigger to commercial reality




R&D Utility of Genome Editing
has achieved phase of
Enlightment & Productivity

Commercial Use of Genome Editing
still needs signifcant progress in adjacent fields to enable
“Robust Breeding Tools“ & “Commercially Valuable Traits“

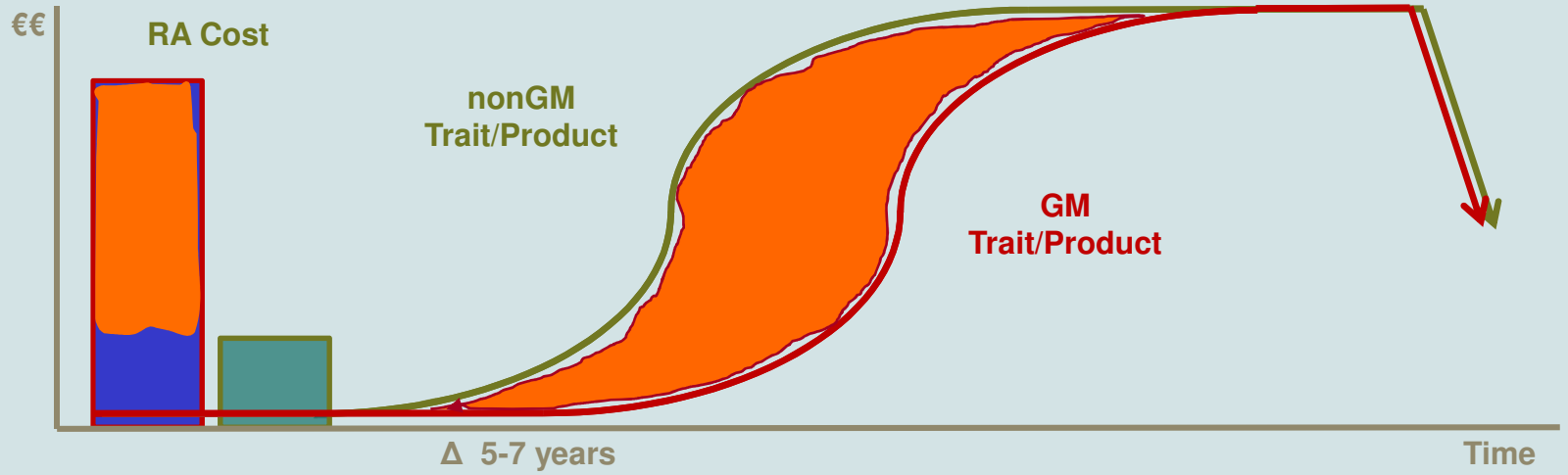
Gene Knock-out/down >> Custom Gene Modulation
Random Indels >> Targeted Mutations & Targeted Insertions

# Genome Editing Technology
## Potential economic benefits nonGM traits & breeding tools

**Genome Editing holds the potential to replace or complement "GM Trait & Breeding Tool Development" with "nonGM Trait & Breeding Tool Development"**

**substantially reduced regulatory cost & time to market**

**higher, longer term earnings impact**




**Lower Regulatory Costs**
**Shorter Time to Market**

**Longer Product Protection**
**Realisation Trait Opportunity**

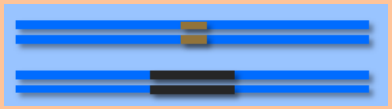
**Higher raNPV & ROI of Trait/Product Concept**

**Secure Trait/Product Market Opportunity**

**Lower Trait/Product Development Cost**

**Higher Overall Trait/Product Revenues**

# Genome Editing Technology
## Opportunity to create variety of traits & breeding tools

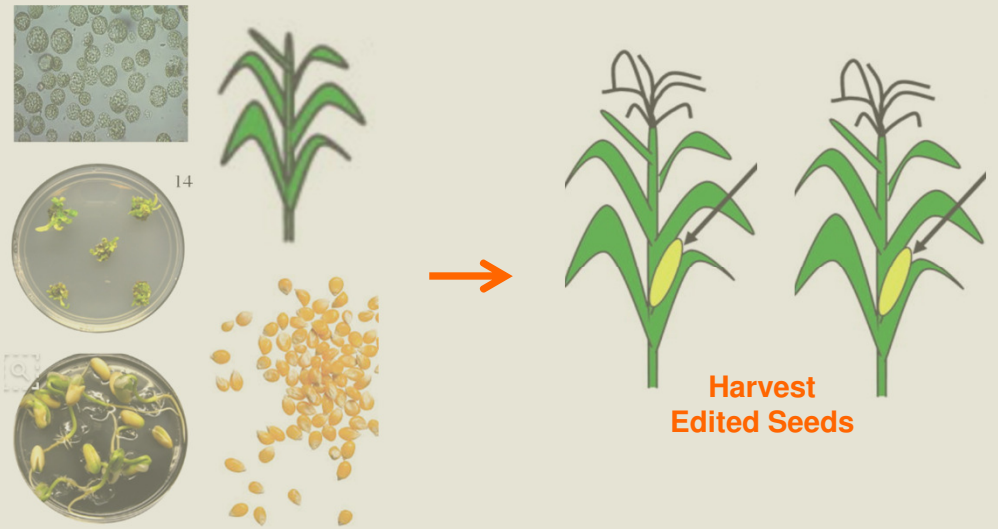
| TARGETED MODIFICATION | EFFECTS | TRAIT & TOOL DEVELOPMENT | DONOR DNA | NON GM |
|---|---|---|---|---|
| **SMALL-LARGE DELETIONS**<br>*(coding & regulatory elements)*<br>  | **Gene Removal**<br>**Gene Knock-out**<br>**Gene Expression Levels**<br>(up / down regulation) | **Biotic Stress Resistances**<br>Herbicide Tolerance<br>Insect, Fungal, Virus Resistance<br>…<br>**Abiotic Stress Tolerances**<br>Drought Tolerance<br>Nutrient Utilization<br>…<br>**Processing & Quality Traits**<br>Bruising, Reducing Sugars<br>Acrylamide<br>…<br>**Breeding Tools**<br>Double Haploid Production<br>Linkage Drag Removal<br>Selectable Marker Excision<br>Custom SNP Markers<br>Modulation Gene Recombination<br>… | - - | US<br>EU<br>ROW |
| **SINGLE-MULTIPLE MUTATIONS**<br>*(coding & regulatory elements)*<br>  | **Gene knock-out**<br>**Gene Expression Levels**<br>**Gene Expression Patterns**<br>**Modification Gene Function**<br>(receptor / ligand affinity) | | - + | **US**<br>EU ?<br>ROW ? |
| **SMALL & LARGE INSERTIONS**<br>*(coding & regulatory elements)*<br>*(NHEJ / HDR)*<br>  | **Gene knock-out**<br>**Gene Expression Levels**<br>**Gene Expression Patterns**<br>**Modification Gene Function**<br><br>**Gene Insertion & Replacement**<br>(within / accross species) | **GM Trait Development**<br>Foreign Gene Insertion & Replacement<br>Native Gene Insertion & Replacement<br>…<br>**Breeding Tools**<br>Native & Transgene Landing Platforms<br>One Step Gene Conversions<br>Custom Stacking of Genes<br>… | + + | US ?<br>EU ?<br>ROW ? |

# Genome Editing Technology
## Transient delivery & expression of genome editing machinery

**Transient Delivery & Expression of Genome Editing Machinery**

**In Vitro**
Cell & Tissue Culture Systems
Immature Embryos
Immature Seeds

**In Vivo**
Vegetative Meristems Young Plants
Generative Meristem Mature Plants
Meristems Mature Seeds
Reproductive Cells - Pollen




**One Step Whole Plant Genome Editing with GM & nonGM Utility**

**Deletion/Mutation Modulation of Native Gene Expression & Function**

**NHEJ/HDR Insertion/Replacement of Transgenes or Native Genes**

**Potential Advantages In-Vivo NHEJ/HDR Gene Insertion**

| In-Vitro Gene Insertion (Cell/Tissue Culture) | | In-Vivo Gene Insertion (Whole Plant) |
|---|---|---|
| Agrobacterium | Genome Editing | Genome Editing |
| GM | nonGM | nonGM |
| Random | Targeted | Targeted |
| Genotype Dependent | Genotype Dependent | Less Genotype Dependent |
| Backcross Line Conversion | Backcross Line Conversion | One Step Elite Line Conversions |

# Genome Editing Technology
## Current limitations to achieve full commercial potential



**GE Complex Delivery**

cells – tissues - meristems
somatic - germline
virus - virus load
vector - integration
gene gun - efficiency

**Cell/Tissue Regeneration**

crop dependency
genotype dependency
robust in-vitro regeneration methods

**GE System Development**

integrative vs transient
in-vitro vs in-vivo delivery
NHEJ / HDR Insertion
meiotic cell systems

**Robust Commercial Utility & Application**

**Trait/Tool Targets**

genes & promoters
gene regulatory networks
epigenetic modifications
signal transduction
knock-out/down

**Regulatory Regime**

integrative vs transient
native - plant - microbial elements
global harmonisation

**Freedom to Operate**

GE Enabling Technology
GE R&D Tools
GE Traits/Tools Targets

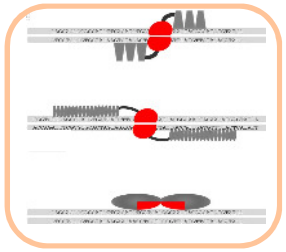
# Genome Editing Technology
## Patent landscape Genome Editing technologies

**Zinc-Finger Nucleases**
Dow Agrosciences (Dupont-Pioneer)

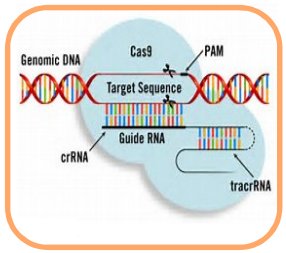
**Mega Nucleases**
Precision BioSciences

**CRISPR-CAS9 Systems**
UC Berkeley; MIT/Harvard
ERS Genomics; Toolgen
Wageningen; Vienna
Vilnius; Target Gene (Dupont-Pioneer)

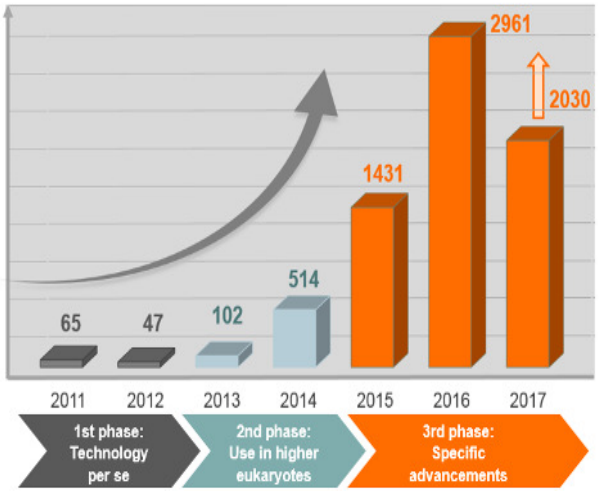
**CRISPR-Cpf1 System**
MIT/Harvard
CRISPR-Cms1 / MAD7 System
Benson Hill / Inscripta

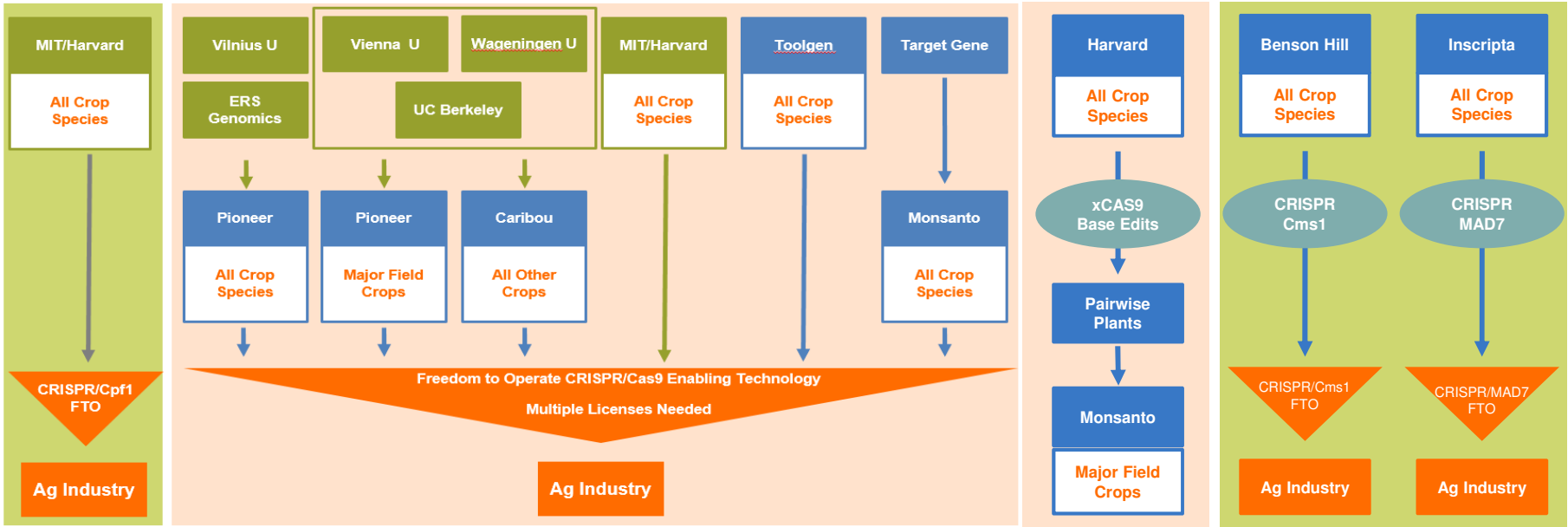


**TALE Nucleases**
Cellectis
Calyxt




**Next Generation GE Systems**
Homologous Recombination
? Others ?



# GE Trait & Technology Development @ KWS

## The Ideal Genome Editing System

- Robust In-vitro / In-vivo delivery to target cells & tissues
- Robust Transient Expression of GE Machinery in cells
- No Integration GE Machinery into the Plant Genome
- Robust ratio-based cell/tissue regeneration systems
- Species/genotype independent editing & regeneration
- No pathogen sequences vis-a-vis regulatory limitations

## KWS Genome Editing Targets

- Yield: Photosynthesis, Source-Sink Physiology
- Abiotic Stresses: Moderate Drought, Nutrient Utilization
- Biotic Stresses: Weeds, Insects, Fungi & Viruses
- Breeding Tools: Doubled Haploids, Hybrid Systems, Targeted Gene Conversion & Stacking, Marker & Linkage Drag Excision, Custom Recombination & SNPs

## GE Enabling Technology Priorities

- Transgenic >> Transient delivery systems
- Transient In-vitro >> Transient In-vivo delivery systems
- High efficiency targeted & custom indels/mutations
- High efficiency targeted NHEJ/HDR template insertion
- Next generation custom GE systems
  *(plant endogenous nucleases & meiotic cell systems)*

## Adjacent Technologies Priorities

- Gene Function & Gene Regulatory Networks
- Gene components & gene epigenetic modifications
- Signal transduction pathways & receptor biology
- Robust, rational cell & tissue regeneration protocols
- Genotype independent cell & tissue regeneration
- DSB repair & recombination > NHEJ/HDR optimization

# KWS innovation strategies
## Partnering approaches & opportunity mapping



**Build unique proprietary positions in strategic crops, traits & technologies**

**Value creation through product development and cross-licensing deals**

**Systematic big data mining to identify & map innovation opportunities**

**Personal relationships in the scientific & venture capital community**

# KWS innovation strategies
## KWS strategic focus & modes of collaboration

## Strategic Focus

**Yield Per Se**
yield components
photosynthetic efficiency
starches, sugars, fatty acids

**Biotic & Abiotic Stresses**
weeds, insects, fungi, viruses, nematodes
drought, nutrient utilization

**Breeding Tools**
molecular markers & genomic selection
doubled haploids & hybridization technologies
plant transformation & transient genome editing
trait conversion efficiency

**Quality Characteristics**
digestibilty & processing
nutritional value

**Seed Treatments**
agrochemicals & biologics
(bio)stimulants & (bio)pesticides

**Precision Agriculture**
field phenotyping & connectivity
farmer platforms

**Big Data**
data solutions & decision making
competitive intelligence

## Modes of collaboration

| | | |
|---|---|---|
| Fee-for-Service Programs | Equity Investments | Evaluation/Validation of Concepts |
| Funded R&D Programs | Joint Venture Formation | Support of POP / POC Studies |
| Joint Development Programs | Company Acquisitions | Exchange of Technology/Datasets |

# Thank You For Your Attention