



**UNIDO Session on Utilization of plants for non-food uses:
Challenges and perspectives – March 3, 2010**

Biodiversity-related Bioenterprise Development in Brazil

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Contributed by  **EXTRACTA**
MOLÉCULAS NATURAIS S/A



BIODIVERSITY-RICH REGIONS IN BRAZIL



- **22% of the Global Plant Biodiversity**
- **>60.000 Species of Vascular Plants**

Under 1500 plant species are documented by Brazilian Traditional Medicine (W.B.Mors et al, 2000). Could modern bioresearch and biotechnologies add significantly to potential pharmaceutical value?



ADDING PHARMA VALUE TO BIODIVERSITY

■ **REGULATORY BACKGROUND**

- CBD and National Control over Biodiversity
- Brazilian Legislation: CGEN/MMA and Special License for Collection
- Landholder Informed Consent prior to Access

■ **ASSEMBLING THE SCREENING COLLECTION**

- Expeditions, Extraction Centers, Dry and Fluid Extract Storage

■ **SCREENING**

- Target Selection, Bioassay Development, High Throughput Screening

■ **DEVELOPMENT OF PROVEN BIOACTIVES**

- Phytotherapeutics and Pure Molecules: funding of Innovation in Brazil

■ **HARNESSING RAW MATERIAL SUPPLY & RETURN OF BENEFITS**

- Plant Identification, selection, multiplication and agro-forestry

■ **TOWARDS THE MARKET**

- Medical Ethics and Regulatory Control by National Agencies
- Pre-Clinical and Clinical Testing
- Licensing and Commercialization Contracts: IP Issues



ASSEMBLING
THE SCREENING
COLLECTION

THE EXTRACTA BANK OF CHEMICAL BIODIVERSITY

- 215 Expeditions covered ~10,000 km² of Atlantic and Amazonian Rainforests in Brazil during 1999-2010.
- 4,905 Plants were collected under rigorous control (GPS, local Digital Photos, Herbarium Samples). Small extraction samples from plant parts averaged 2.5kg.
- 11,586 TLC-controlled etanolic extracts yielded 31,492 chemical samples for HTS screening campaigns against targets of interest.
- A unified data base controls the Bank and screening results (proprietary software).



ASSEMBLING THE SCREENING COLLECTION

**RIO DE JANEIRO & BELÉM:
extraction facilities can process up to 15.000 extracts per year**

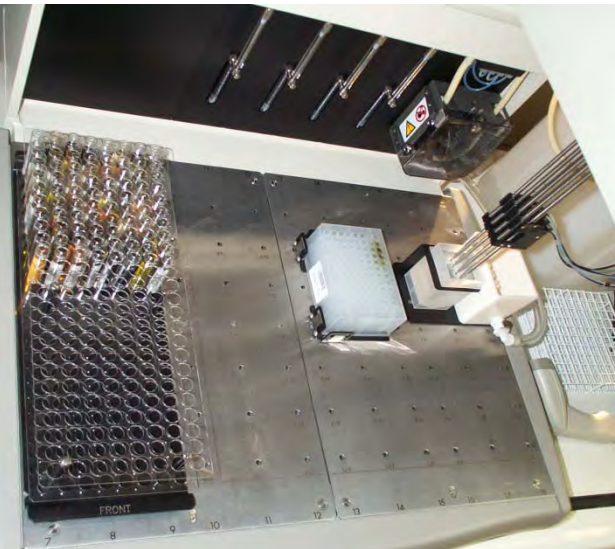


**Extracts
are stored
at – 30°C
until use**



TARGETTING BIOACTIVITY WITH HTS SCREENING

- **Target choice and Bioassay development**
 - **Extract dispensation in 96-well plates**
 - **Plate reorganization after HTS results**
("cherry picking")





TARGETTING BIOACTIVITY WITH HTS SCREENING

Medium-High Throughput Screening at EXTRACTA: up to 24,000 operations daily

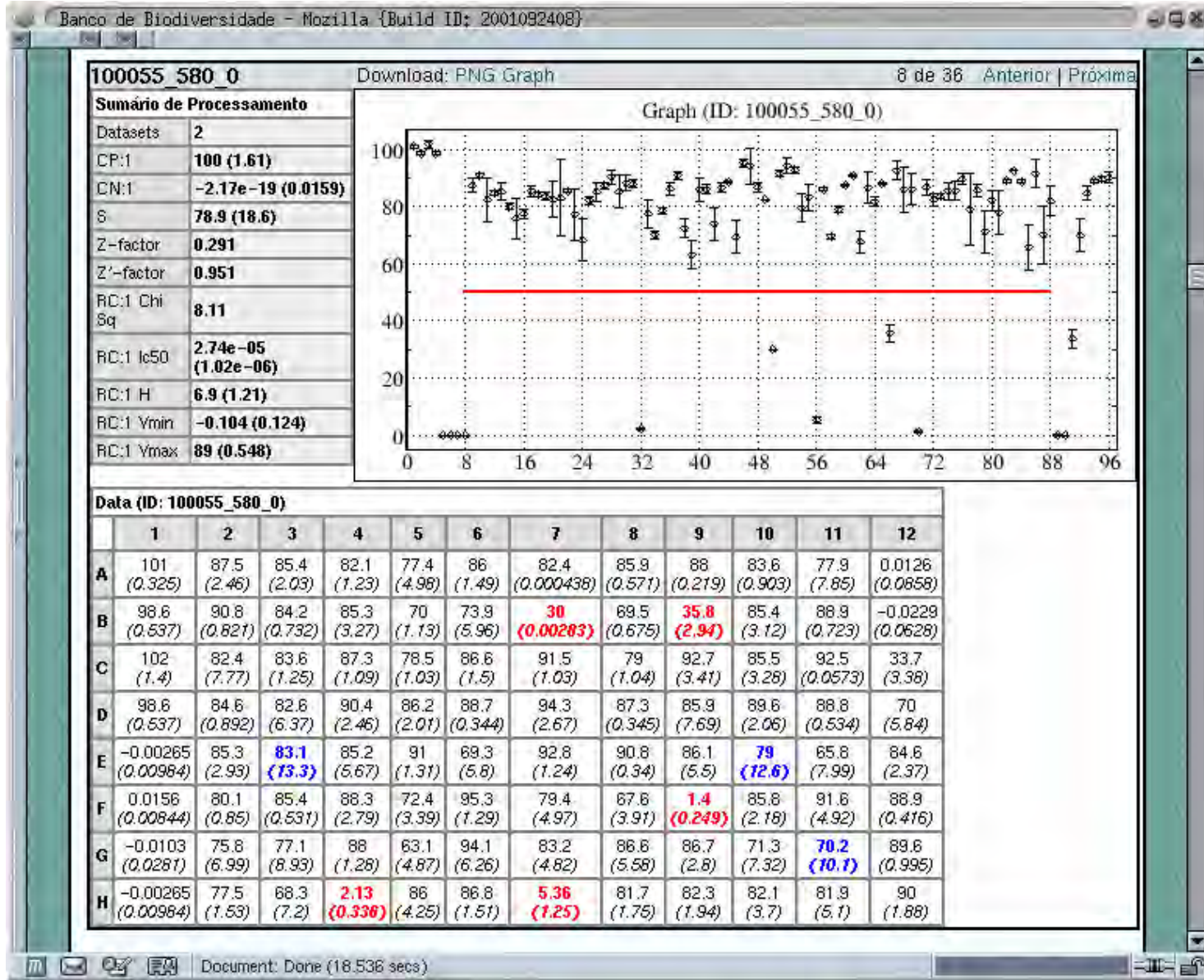




TARGETTING BIOACTIVITY WITH HTS SCREENING

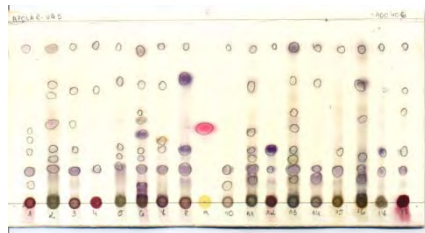
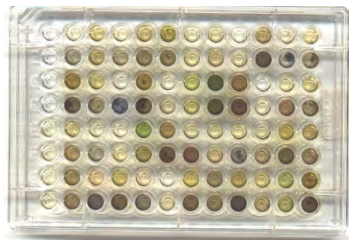
Target: xxxx
 Assay: xxxxx
 Run: Screening 1
 RI: xxxxx
 DIPlateID: 100055
 2 assay plates in duplicate
 Z' factor: 0.951
 X²: 8.1
 RI Ic50: 2.7e-5 M

DATA PROCESSING





BIODIRECTED CHEMICAL FRACTIONATION



- 1) Tannin score and removal
- 2) TLC quality control
- 3) Biodirected Extract fractionation in search of active compound

- UV-visible spectrometry and HPLC

- **High definition LC-MS**

- **NMR experiments**

- **X-Ray Crystallography**



OUTSOURCED





EXTRACTA INNOVATION PIPELINE

EXTRACTA PIPELINE: POSITIVE HITS NEED FINANCING TO RETURN BENEFITS LOCALLY

Target Pathology	Primary Bioassay	No. of Strongly Active Extracts	No. of Purified Active Fractions	Pure Isolated Compounds (95% Pure)	
Resistant Hospital & Community Infections	Meticillin - resistant S.Aureus (MRSA)	49	12	3	
Disease (DPOC)	Elastase inhibition	32	18	7	
Hepatitis C	Cell Protection against surrogate target	118	12	NA	
Chagas Disease	Cruzipain inhibition	98	2	NA	
Tuberculosis	InhA inhibition	38	13	NA	
Diabetes Type II	PTP-1B inhibition	348	NA	NA	
Development Candidate Extracts		683	<i>In yellow: Innovation Projects Financed by Brazilian Agencies FINEP and FAPERJ</i>		



ANTI-MRSA SELECTED CRUDE EXTRACTS

MIC Comparison between 3 selected extracts and a Commercial Antibiotic against Meticillin-resistant *S. aureus*

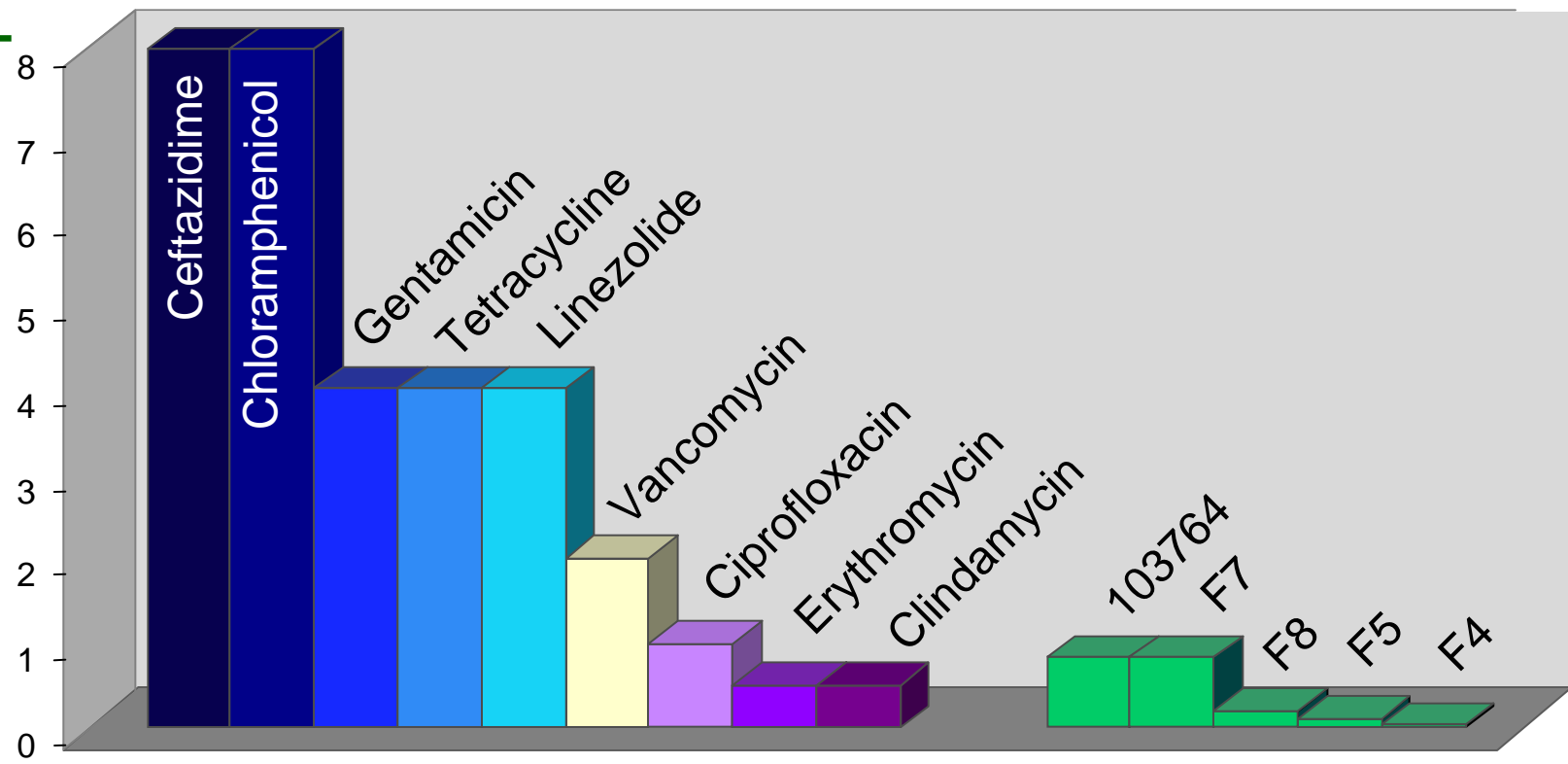




ANTI-MRSA EXTRACTS, FRACTIONS AND PURE COMPOUNDS

MIC of Extract 103764 and its purified Fractions compared to Commercial Antibiotics

MIC
 $\mu\text{g/mL}$





EASTERN AMAZONIAN
JOINT VENTURE
(ONGOING MODEL)

Public Herbarium (Goeldi Museum)

Collectors

**EXTRACTA
(Licensed
by CGEN)
And UFPA**

**R&D
Contracts**

Academia

Partnerships
in R&D&I

Patents

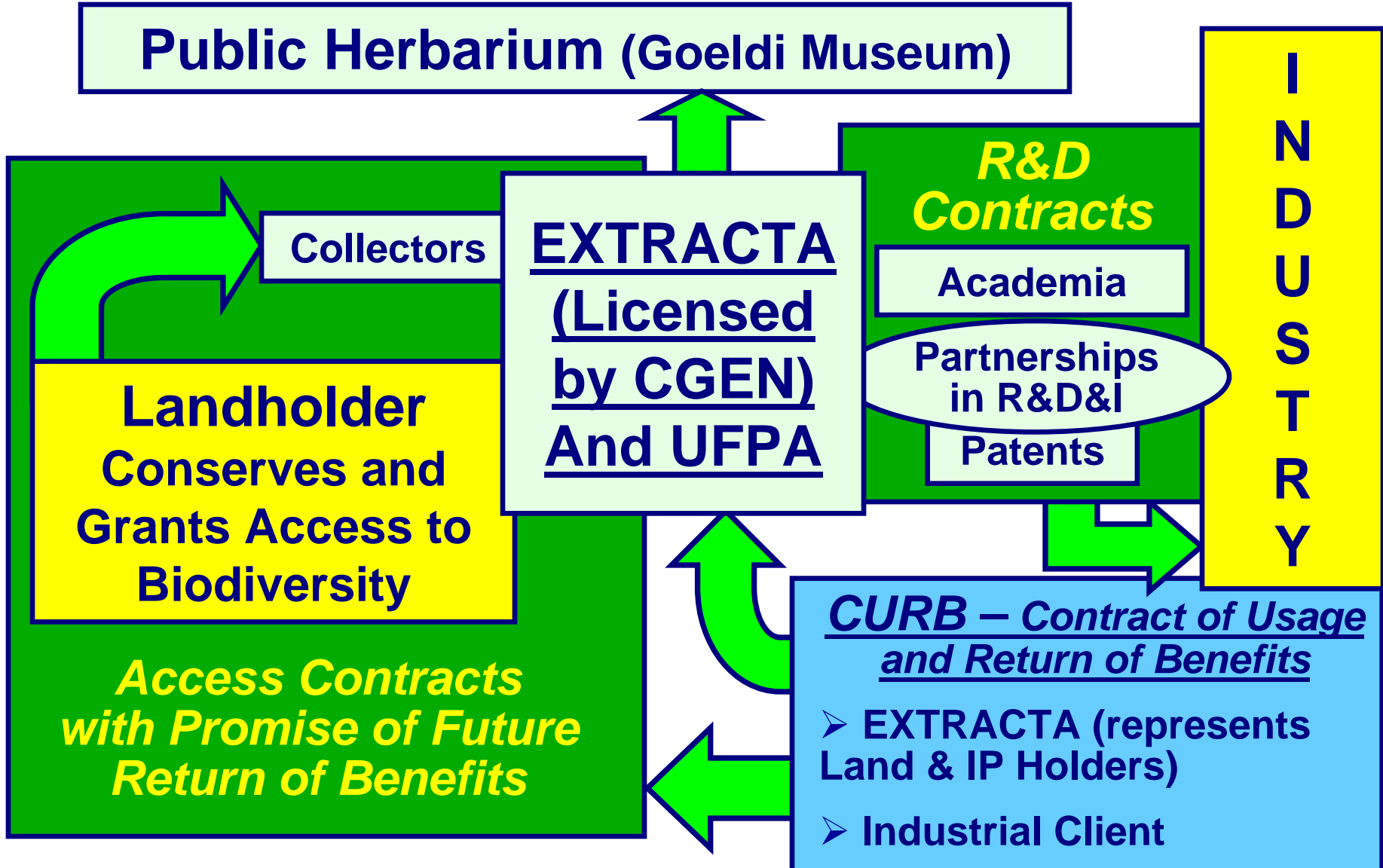
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**Landholder
Conserves and
Grants Access to
Biodiversity**

**Access Contracts
with Promise of Future
Return of Benefits**

**CURB – Contract of Usage
and Return of Benefits**

- EXTRACTA (represents Land & IP Holders)
- Industrial Client





HARNESSING RAW MATERIAL SUPPLY & RETURN OF BENEFITS (I)

■ CLONE BOTANICAL CLASSIFICATION

- Phylogeographic and biodiversity study
- Macro and microanatomical study of “plant drug”
- DNA “fingerprinting”

■ CLONE CHEMISTRY AND BIOACTIVITY

- TLC, SPE, Column Chromatography & HPLC
- Isolation of Bioactive Plant Marker (95% Purity)
- Bioactive Compound Structure

■ CLONAL MULTIPLICATION

- Agricultural (cuttings & other)
- Micropropagation by Tissue Culture



HARNESSING RAW MATERIAL SUPPLY & RETURN OF BENEFITS (II)

■ **AGRO-FORESTRY STRATEGY**

- **Agro-Forestry Engineering Plan Approval (StateLevel)**
- **Local Aclimatization of Cloned Plantlets at the Farm**
- **Farm Experimental and Producing Clonal Orchards**
- **Underbrush Enrichment with Clones in the Neighborhood of Original Plant Access**

■ **CGEN-ASSISTED INDUSTRY-EXTRACTA CURB**

- **The Important Issue of Intellectual Property in PHARMA and the Brazilian Approach to the Solution**
- **Returning Benefits to the Farmer: Engineering of Clonal Planting and Production; Commercialization Goals and Pre-Set Prices; Technology Transfer through Training of Extensionists and Farmhands**
- **Returning Benefits to Associated Institutions and Inventors**



EXTRACTA IS THE RESULT
OF THE CONCERTED
EFFORT OF MANY...

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