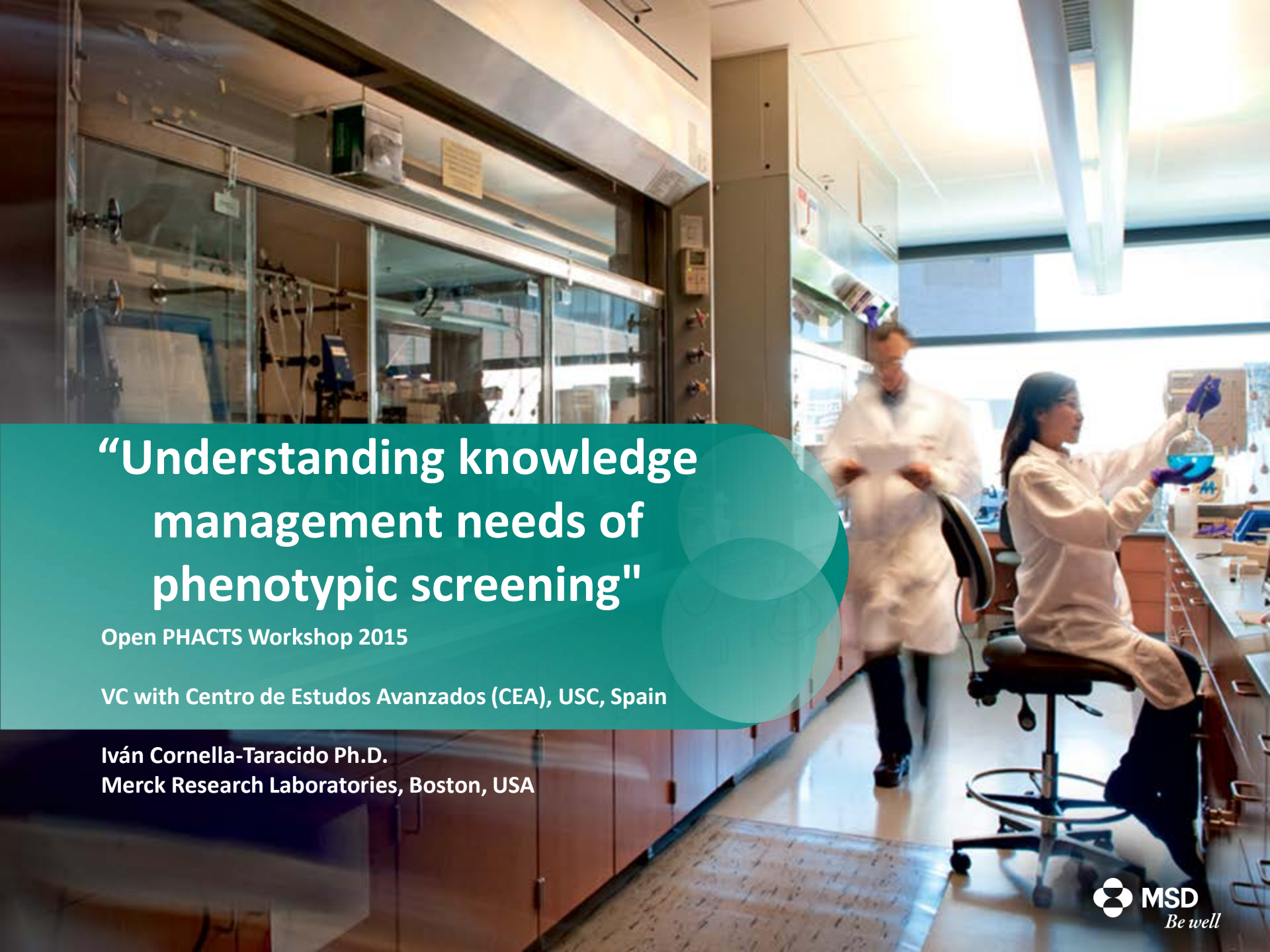

“Understanding knowledge management needs of phenotypic screening"

Open PHACTS Workshop 2015

VC with Centro de Estudos Avanzados (CEA), USC, Spain

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MSD
Be well

Challenger Introduction: Iván Cornella
Short Bio. Connection to phenotypic screening

Current Position: Sr. Principal Scientist, Discovery Chemistry, Merck Research Laboratories, Boston, USA.

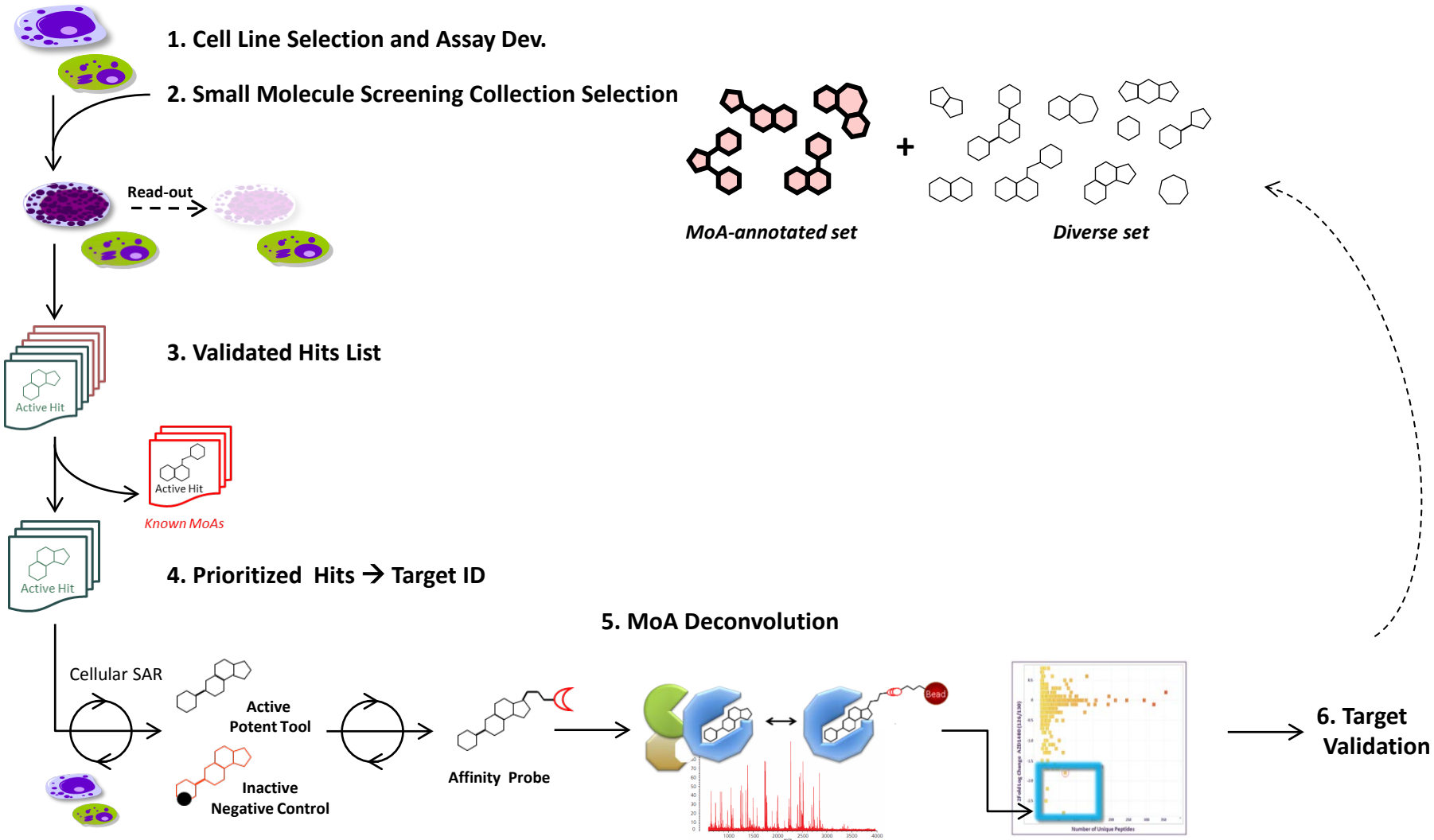
- Co-chair of the MRL phenotypic screening initiative
- Chemical Biology Lead, member of the Capabilities Enhancement team.
- Accountable for the implementation of the MRL Chemical Biology strategy to support target identification and validation.

Prior positions: Assoc. Director Discovery Sciences-CIC, Head Chemical Biology, AstraZeneca., Boston, USA.
Head Chemical Biology, Sanofi Oncology, Boston, USA.
Chemical Genetics and Proteomics Laboratory Head, Novartis Inst. BioMed. Res. (NIBRI), Boston, USA.

- Responsible for leading phenotypic and signaling pathway screen hits towards mechanism of action elucidation and validation, using chemical genetics and chemoproteomics techniques, integrating medicinal and synthetic chemistry with molecular biology, pharmacology and informatics in a multidisciplinary team effort.
- Contributor to the elucidation of the mechanism of action of natural and synthetic bioactive small molecules and the adoption of novel targets in the early drug discovery portfolio of multiple disease areas.

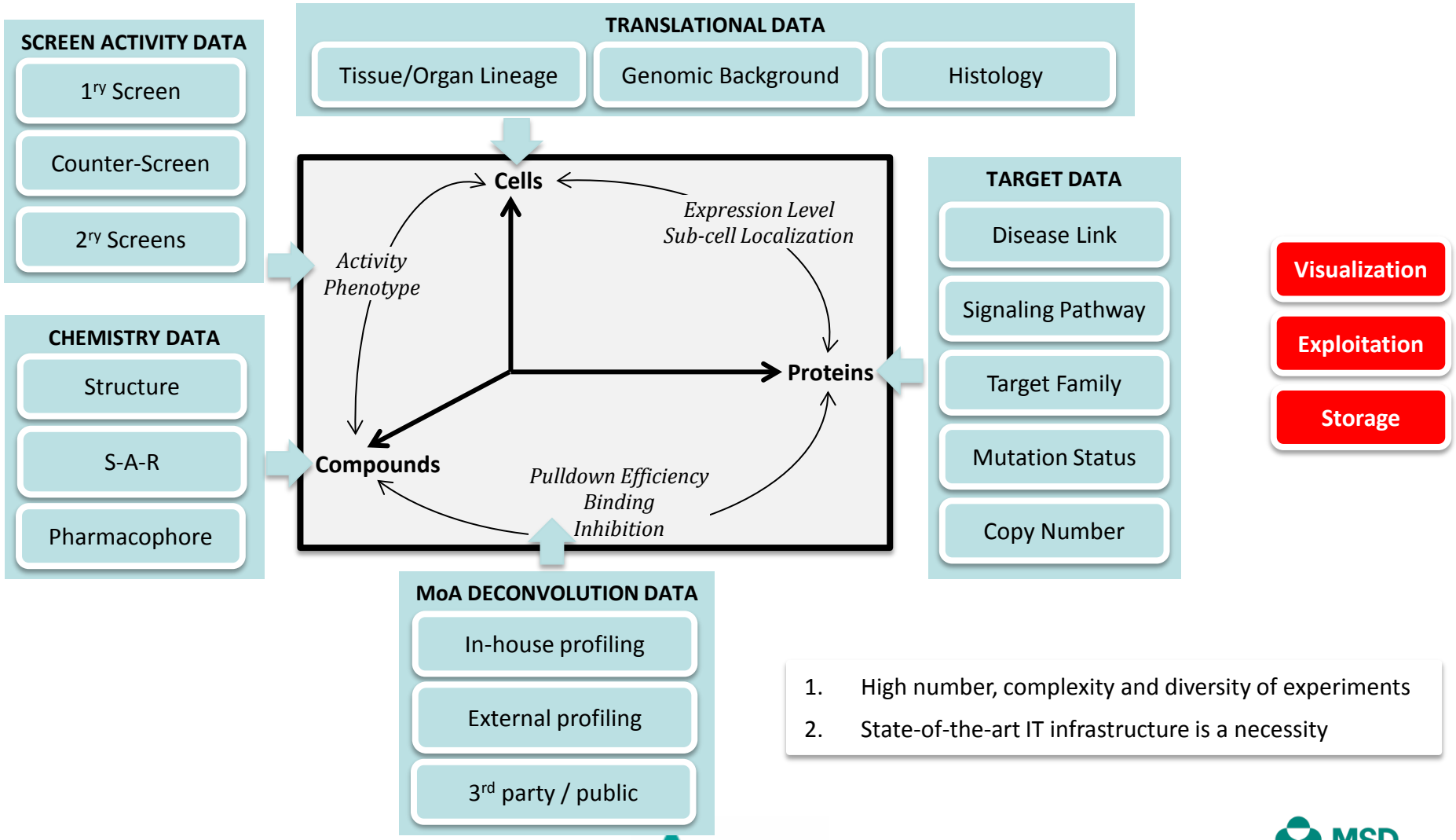
Phenotype-driven Target Discovery Workflow

Enabled by close collaboration between disciplines



Phenotypic Target Discovery is data intensive

Disease × Cells × Compounds × Proteins



1. High number, complexity and diversity of experiments
2. State-of-the-art IT infrastructure is a necessity

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Phenotypic screening and target discovery

Knowledge management needs

1. **BEFORE the Screen**
   - 1.1. The right "line of sight" hypothesis to address an unmet medical need
   - 1.2. The right assays: Robust and disease-relevant ("translation-able") **(Investment Decision 1)**
   - 1.3. The appropriate Read-out(s)
   - 1.4. The right screening deck (throughput, modality, special decks) – MoA-annotated sets **(Investment Decision 2)**
   - 1.5. The right workflow plan for triaging and advancing hits (selectivity & translatability)

2. **DURING the Screen**
   - 2.1. What is a hit?
   - 2.2. How do we prioritize hits? And how many? **(Investment Decision 3)**
   - 2.3. Cellular SAR: Strong understanding of SAR (including +/- control analogs)
   - 2.4. Cellular selectivity: Well-established through appropriate triaging and counter-assays

3. **AFTER the Screen:**
   - 3.1. Target Deconvolution. Which tactic(s) to choose and when? **(Investment Decision 4)**
   - 3.2. Target identification Affinity Probes
   - 3.3. Knowledge to prioritize Protein target(s)
   - 3.4. Target Validation

Big Data solutions for target discovery

Finding inspiration in APEs

The **Analogous Problem Exploration (APE)** concept:

"Stop thinking about how to solve your problem with your currently available tools and look for other's solutions to similar challenges"

Premise: Instead of trying to solve the large, complex data problems of target discovery *only* from within, is there another industry that deals with a similar challenge?

Example 1: The oil industry.
How do they map oil fields to find new wells? Using booms, cables and air guns, with tens of thousands of sensors that record data 2 or 3 times per minute, they need to analyze trillions of pieces of data, from which most is noise, to separate the good from the bad before they may the financially and temporally committed drilling investment.

Example 2: Space exploration for exoplanets that may host new life forms.
How do they decide which data to capture, or how to separate background noise from very weak signals?

Challenge: Do these problems resemble ours?
What can we learn from these APEs to facilitate next generation knowledge?