Innovative Medicines Initiative

APPROACH – Applied Public-Private Research enabling OsteoArthritis Clinical Headway

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Burden of Disease: Osteoarthritis

Osteoarthritis is the most common global arthritic disease and is becoming more prevalent as the population ages and obesity rates rise.

- OA is already ***one of the ten most disabling diseases*** in developed countries
- Between 2002 and 2007, OA moved from the twelfth to the ***sixth leading cause of years lost to disability or morbidity*** (WHO data), and between 1990 and 2010, OA moved from fifteenth to the ***eleventh leading cause of years lived with disability (YLDs)*** – Global Burden of Disease Study 2010.
- History of joint injury and manual labour increase risk, as do age, obesity and sedentary lifestyle
- Global estimates are ***that 9.6% of men and 18.0% of women over 60 have symptomatic OA***
- 80% of those with OA will have limitations in movement and 25% cannot perform their major daily activities of life

Direct and indirect costs of OA for the EU are substantial; ***in the UK alone, total costs are estimated to be equivalent to 1% of the gross national product (GNP) per year***.

Problem Statement: APPROACH

Despite a large and growing disease burden, many pharmaceutical organizations have de-emphasized or abandoned osteoarthritis (OA) drug development due to real and perceived hurdles. Ultimately, a number of highly visible and costly failures have highlighted the scale of the challenge and subsequently reduced the number of companies independently pursuing the development of disease modifying OA drugs (DMOAD).

Contributing factors include:

- Incomplete understanding of OA pathogenesis
  - Heterogeneous disease with a variety of pathophysiologic drivers
- Assumption that treatments will work across most patients
  - Clinical development plans have frequently used a 'one size fits all' approach rather than matching mechanism of action to specific OA patient subpopulations (i.e. personalized medicine)
- Reliance on relatively insensitive endpoints
  - X-ray-based joint space narrowing (the current standard DMOAD endpoint) is insensitive, tends to be slowly evolving and does not allow visualization of the tissue most associated with the disease (cartilage)

Considering the scale of the problem and societal impact, there remains a major unmet need as current treatments are predominantly restricted to symptomatic relief or costly and invasive surgical intervention.

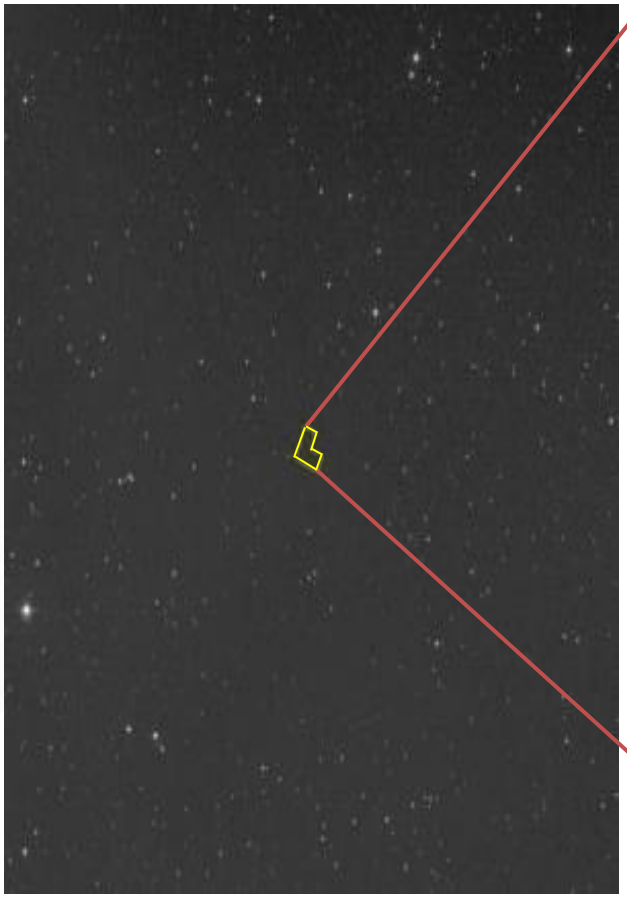
APPROACH Foundational Hypothesis

- OA is a heterogeneous condition with a variety of pathophysiologic drivers that can lead to disease and disability, some more amenable to pharmacologic therapy than others

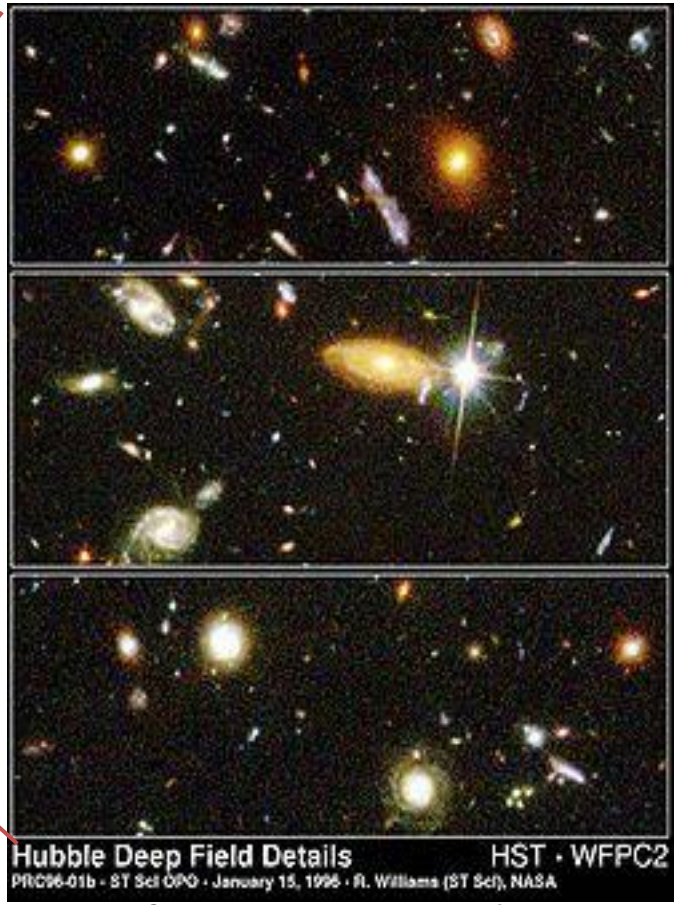
- Identification of patient subsets and related etiologic factors will enable clinical trial efficiency and lead to safer and more effective therapeutics

The challenge of treating OA depends on perspective

Daunting?



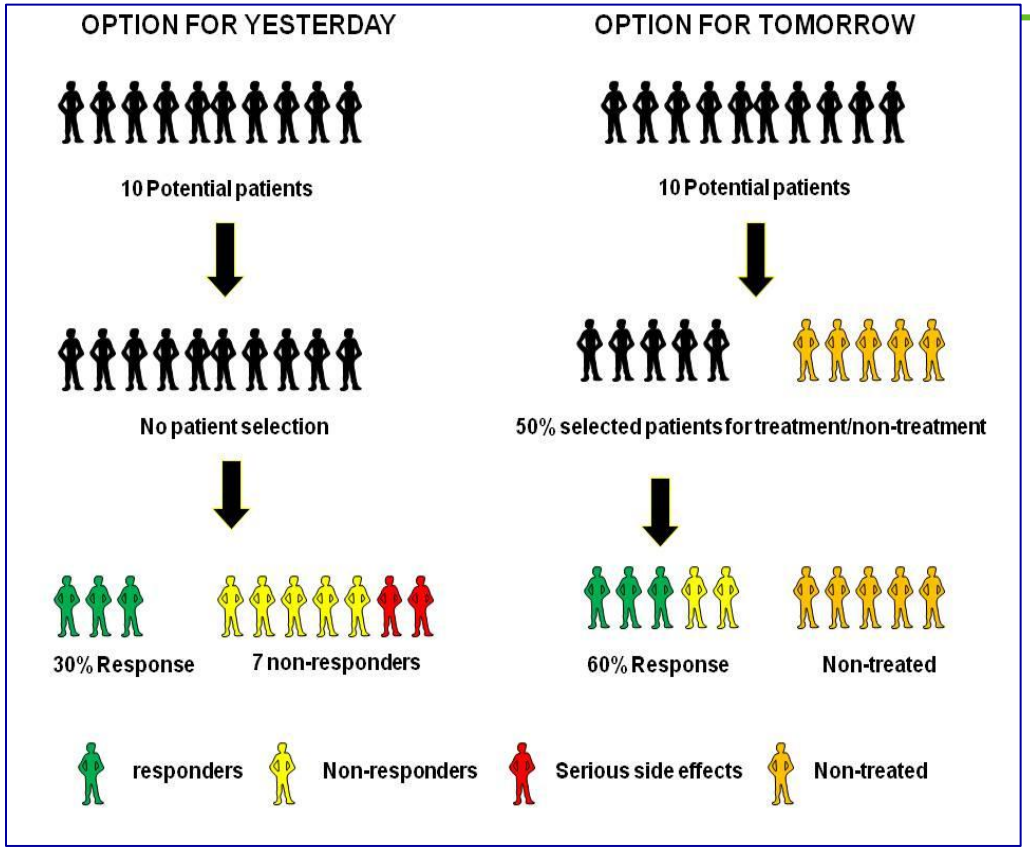
Opportunity?



Defining Patient Subsets

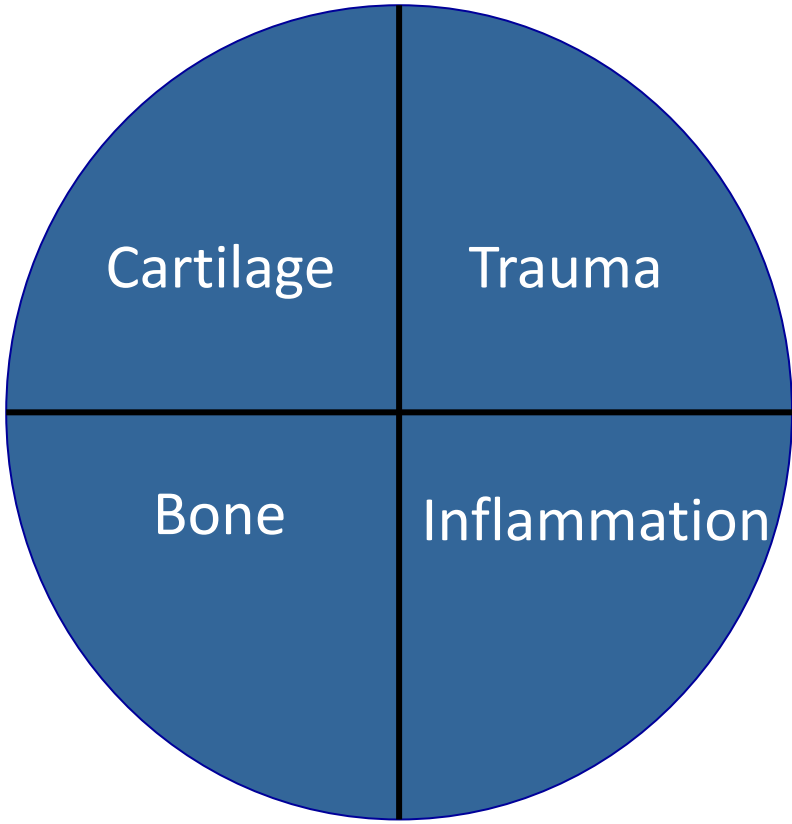
The Case for Stratification in OA

Increased response and decreased risk



Nature Rheumatology, Karsdal et al, 2013

OA patient segments: Phenotypes



Need for public-private collaboration

The issues in OA drug development are large and complex and independent effort has led to slow clinical progress. These challenges can be best addressed by a major Public-Private-Partnership of engaged, knowledgeable and complimentary industrial and academic experts who can provide innovative and viable solutions.

Objectives of the full project

1. Implement comprehensive and high quality biomarker assessment to characterise OA patient subsets and support future regulatory qualification and endpoint validation

2. Provide framework to identify the “right patient” to treat for a given drug
   - Link OA patient subsets to potential DMOAD targets based on phenotypic biomarkers, highlight specific disease drivers and progression criteria

3. Build stronger collaborations within and among academic and industrial groups to enable future OA therapeutic development

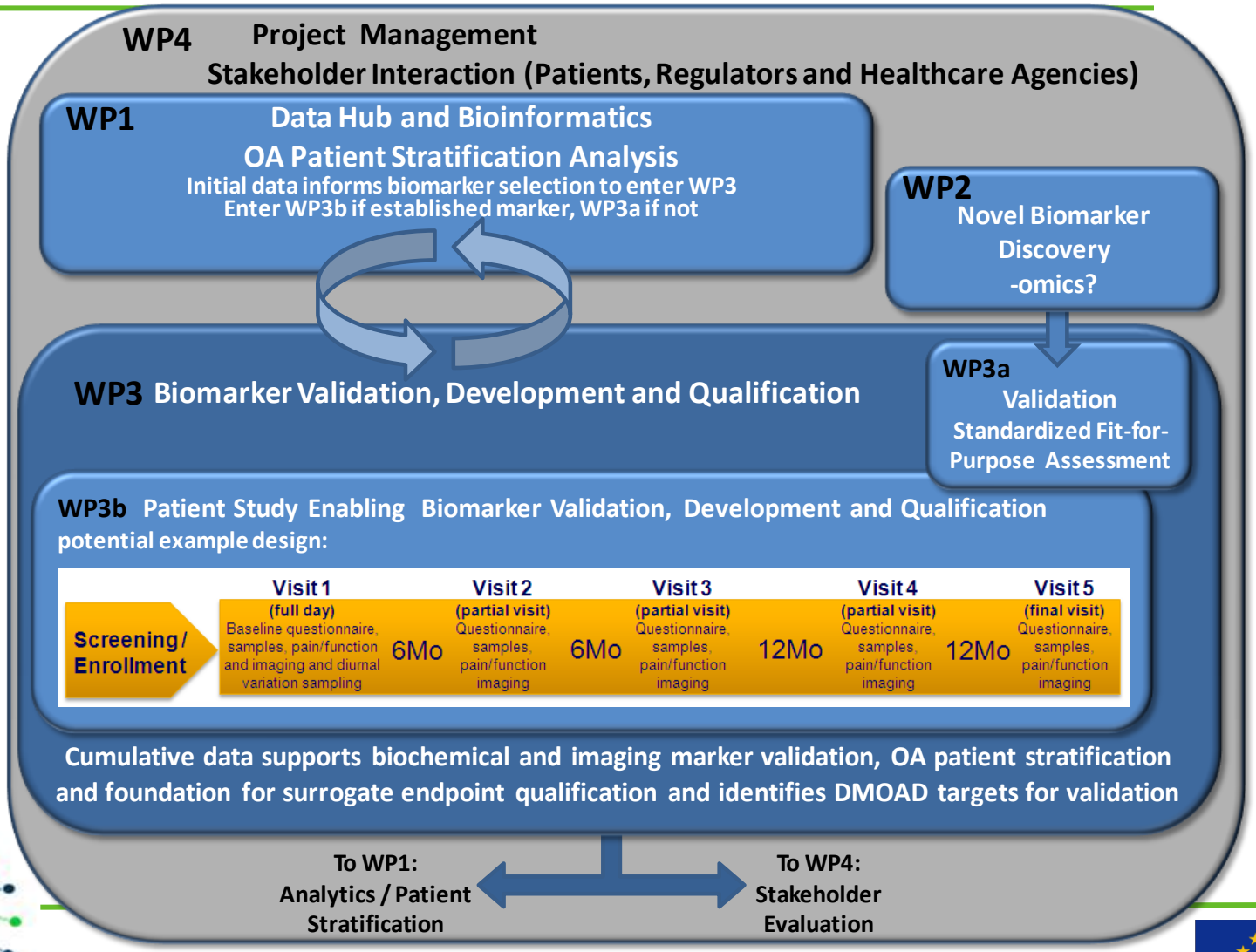
Pre-competitive nature

Goal: To enable streamlined and focused DMOAD clinical testing by defining OA patient subsets by demographic, biochemical and imaging parameters and setting the foundation for regulatory qualification.

Complementary to numerous other efforts

- **TreatOA** – EU - FP7 funded initiative
  - Access to 28,000 patient cohort and control subjects
  - Largely genomics driven (GWAS and functional genomics)
  - Limited set of biochemical markers included
- **CHECK cohort** – Dutch Arthritis Association funded
  - 10-year (~1000 participant) prospective hip and knee OA study with radiographic and biological samples
  - Many biochemical markers assessed
- **Osteoarthritis Initiative (OAI)** – NIH/Industry funded (incl. GSK), publically accessed
  - 6-year (~4800 participant) prospective study of knee OA patients, 'at risk' individuals and controls
  - Baseline and annual biological sample collection, demographics and imaging (radiograph and MRI)
  - fNIH consortium substudy currently profiling 12 biochemical markers to assess rapid image-based progressors
- **Nationalen Gesundheitsforschungsinitiative Arthrose (NGFA)** Germany based OA cohorts
- **Also, DOXY, KHOALA, Johnson county, etc.**

Suggested architecture of the project



Expected contributions of the applicants

- Workpackage co-leadership (WP1-4)
- Statistical expertise (WP1)
- Existing biochemical marker data (WP1)
- Clinical centre with required infrastructure (WP3)
- Access to OA patient cohorts (WP3)
- Imaging and image analysis expertise (WP1-3)
- Biomarker discovery and Omics expertise (WP2)
- Novel imaging modalities (WP2-3)
- Biochemical marker kits/reagents (WP2-3)
- Existing clinical samples (WP3)
- Sample processing/storage expertise (WP3)
- Certified (CLIA) testing lab (WP3)
- Strategic clinical/academic perspective (WP4)
- Strategic patient perspective (WP4)

Expected (in kind) contributions of EFPIA members

- Workpackage co-leadership (WP1-4)
- Statistical expertise (WP1)
- Informatics/IT support (WP1)
- Data Management support (WP1)
- Human Biological Sample Management compliance support (WP1 and 3)
- Biochemical marker expertise (WP1-3)
- Existing biochemical marker data (WP1)
- Imaging/image analysis expertise (WP1-3)
- Biochemical marker kits/reagents (WP2-3)
- Existing clinical samples (WP3)
- Sample handling/storage (WP3)
- Project Management support (WP4)
- Regulatory expertise (WP4)
- Commercial/Payor perspective (WP4)
- Strategic industry/clinical perspective (WP4)

Total EFPIA in-kind commitment = €7.5 million

What's in it for you?

Stakeholders:

- EFPIA Partners
- Public/SME Partners
- External (Regulators, Patient Groups, Research Orgs [EULAR, OARSI, etc], Healthcare Systems)

Some benefits of being a partner in this project

- Collaboration of industry and academic expertise and shared perspectives
- Maintained/enhanced visibility in OA field
- Potential to develop biomarkers of interest
- Early access to data and opportunities to publish
- A 'seat at the table' to guide future strategy
- Enables future clinical development in OA (alone or as an alliance)
- Funding opportunities

Key deliverables of the full project

- A successful outcome will outline a strategy to provide a more tenable pathway to select and clinically evaluate potential DMOADs:
  - Identify and characterise patient subsets
  - Reduction of sample size and duration of POC studies
  - Increase probability of success
  - Extrapolation to general OA population
- Submission of biomarker qualification process(es) to health authorities:
  - Imaging, with a special remark on MRI
  - Biochemical markers
  - Genetic markers for prognosis
- Standardised data packages for comparison and use in regulatory environments
- Creation of a dedicated network of industry and academic expertise

Questions?

- Contact the **IMI Executive Office**

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Website: www.imi.europa.eu