U-BIOPRED

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project update 2013–2014

www.UBIOPRED.eu

U-BIOPRED is an IMI funded project, receiving the support of the EU and EFPIA

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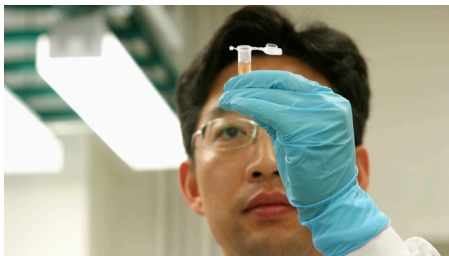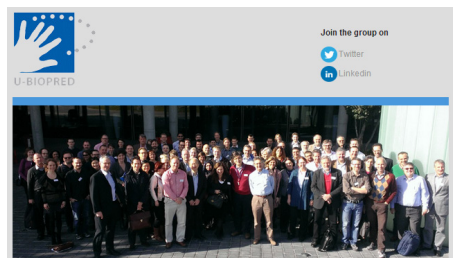
imi
Innovative Medicines Initiative

Introducing U-BIOPRED

What is U-BIOPRED?

U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) is a research project using information and samples from adults and children to learn more about different types of asthma to ensure better diagnosis and treatment for each person.

The main aims of the project are:

- to understand more about severe asthma
- to determine how it differs from person to person
- to uncover new information and ideas that could lead to the creation of effective new treatments
- use advanced mathematics to create U-biopred fingerprints and a 'handprint' of severe asthma sub-types, from omics and clinical data

Major achievements in 2013–14

2013-2014 has seen the U-BIOPRED project mature, with high quality data being rigourously analysed with various approaches. The completion of the clinical trial with severe asthma, mild/moderate and healthy control cohorts and the generation of a first 'handprint' demonstrate how the project has moved towards this final phase.

U-BIOPRED is now in good shape to create further 'fingerprints' of clinical measurements and omics which will feed into a set of four 'handprints', to identify severe asthma phenotypes.

Our major achievements in 2013-14 have been:

- Completion of the clinical trial with 1,029 study participants across 4 adult and 4 paediatric cohorts
  - closure of Longitudinal visits with 80% (in total 517) of the severe asthma study participants in the asthma cohorts returning for their visit
  - exacerbation visits, CT scans and telemonitoring data captured in the adult asthma cohorts
  - healthy volunteer panels complete; proving the infectivity of the rhinovirus used in the viral challenge study
- Part 1 of the WP5 viral challenge study, the safety study, is near completion with asthma panels of 6 study participants now complete
- Clean baseline data made available through the U-BIOPRED tranSMART platform
- The final samples have been received at the biobank. See page 4, 'Developing a biobank'
- Two new opportunities via ENSO grants from the Innovative Medicines Initiative (IMI) have been granted to develop a sustainability plan and to add three extra fingerprints to the study - Microbiome, Analyte set and Metabolomics
- Writing plans have been developed, including the clinical cohort description papers for the adult and paediatric cohorts have been submitted

U-BIOPRED case studies

Developing a biobank

The U-BIOPRED biobank was established to manage the 100,000 samples collected in the project. This significant research resource will be continued beyond the project as part of our sustainability plans. 13 different kits, with a typical kit containing 141 items of pre-labelled labware, were prepared for the main clinical trial, with additional kits created for bronchoscopy visits and the viral challenge study. Each sample received is tracked via the LIMS tracking system.

The biobank is now in the phase of shipping out sample sets to researchers, and managing the return of unused samples. Having a dedicated biobank has allowed the project to implement a complicated clinical trial kit, align the protocol amendments and keep track of the movement of samples between centres.

Patient Input Platform (PIP)

A core element of U-BIOPRED is the involvement of patients, integrating patients into the project from the planning through the analysis stages. Patients are also directly contributing to our Safety Monitoring Board and to the Ethics Board. This philosophy has meant that patients have contributed to the clinical trial protocols and Standard Operating Procedures (SOPs), our sustainability plans and have also been involved in key meetings.

In order to take forward our 'deep integration' approach, the PIP is aiming to continue its work after the project's completion, helping to provide a platform to engage patients in other research projects. This has included involvement in a European level workshop in Brussels in June 2014, organised by EFA (European Federation of Allergy and Airways Disease Associations) and co-hosted by Members of European Parliament Catherine Stihler and Petru Luhan. This workshop allowed researchers and patients to share their visions on how innovative EU-funded research can positively impact the lives of people with lung conditions in Europe, and how meaningful patient engagement in these projects can become a model for the future.

A white paper will be released shortly, further outlining the project's experience in integrating patients into our work. Visit our website www.ubiopred.eu or follow us on Twitter at @ubiopred for updates and more information.

U-BIOPRED at ERS International Congress

Symposia

Asthma phenotyping: collaborative projects in Europe
Monday 8 September, Room A2-4, Session 222 10.45–12.45

Agenda

10:45	**Deep asthma phenotyping: the need to collaborate in Europe** K.F. Chung (London, UK)
11:12	**Understanding severe asthma by linking 'omics' to the clinic: the U-BIOPRED experience** R. Djukanovic (Southampton, UK)
11:39	**Imaging and computational modelling of severe asthma: the AirPROM experience** C. Brightling (Leicester, UK)
12:06	**Big data requires 'big' collaboration** S. Wagers (Maasmechelen, Belgium)
12:33	**A patient's testimony** D. Supple (Brighton, UK)

Chairs P. J. Sterk (Amsterdam, The Netherlands) and L. Heaney (Belfast, UK)

Aims After this symposium the audience will:
• Be familiar with the concept and achievements of personalised medicine
• Appreciate the value added by molecular profiling in terms of phenotyping severe asthma
• Be acquainted with the possibilities of modern imaging for severe asthma phenotyping
• Understand the benefits and pitfalls for both professionals and patients that are associated with collaborating in big consortia

Target audience clinicians, basic scientists, pharmaceutical industry representatives, governmental and policy-making representatives.

Oral presentations and poster discussions

Sunday 7 September

Clustering analysis of clinical variables in U-BIOPRED adult asthma cohort	Room 14c, Session 52 08:30 – 10.30 (presenting at 08.45) Oral presentation
Combined analysis of gene expression and clinical data in the severe asthma U-BIOPRED cohorts	Room A1-1, Session 70 10:45-12:45 (presenting at 11.15) Oral presentation
Unbiased clustering of children with asthma or pre-school wheeze using the U-BIOPRED electronic nose platform	Room 14c (ICM), Session 74 10:45-12:45 (presenting at 11.15) Oral presentation

Monday 8 September

Clinical and histological comparison of smoking and non-smoking patients with severe asthma in the U-BIOPRED cohort	Room A2-2 Session 205 08:30-10:30 (presenting at 09.00) Oral presentation
Discrimination between oral corticosteroid-treated and oral corticosteroid-non-treated severe asthma patients by an electronic nose platform	Room M-2 (B0) Session 240 10:45–12:45 Poster
Whole transcriptome analysis in peripheral blood from asthmatic and healthy subjects in the U-BIOPRED study	Room M-1 (B0) Session 239 10:45-12:45 Poster
Influenza but not Rhinovirus viral strain causes exacerbation of a house dust mite driven severe asthma mouse model	Hall B2-25 Session 263 12:50-14:40 Poster

Tuesday 9 September

Urinary LTE4 is a new strong predictor of TH2-driven asthma: Initial data from the Pan-European U-BIOPRED IMI project	Room A1-1 Session 376 10:45-12:45 (presenting at 11.15) Oral presentation
Corticosteroid insensitivity in airway smooth muscle cells from severe asthma is dependent on stimulus and cytokine product	Hall B2-18 Session 404 12:50-14:40 Poster
Gene set variation analysis of mRNA expression in bron-chial biopsies from the U-BIOPRED asthma study	Room M-1 (B0) Session 365 08:30-10:30 Poster
U-BIOPRED: Clinical characteristics of children with severe asthma (SA) and severe pre-school wheeze (SPSW)	Hall B2-37 Session 423 12:50-14:40 Poster
The U-BIOPRED severe asthma study: Immunopathological characterisation	Hall B2-19 Session 405 12:50-14:40 Poster

Wednesday 10 September

Characteristics of the adult corticosteroid-dependent severe asthma in UBIOPRED consortium	Room 14c Session 508 10:45-12:45 (presenting at 10.45) Oral presentation
ADEPT-derived, U-BIOPRED validated asthma clinical clusters with Th2 and non-Th2 phenotypes	Room 14c Session 508 10:45-12:45 (presenting at 11.00) Oral presentation

Abstract focus

Characteristics of the adult oral corticosteroid-dependent severe asthma in U-BIOPRED consortium

Patients with severe asthma defined according to IMI criteria (Bel *et al.* Thorax 2011; 66: 910-7) often need regular oral corticosteroid (OCS) therapy in addition to inhaled CS. We determined whether OCS-dependent subjects are a distinct group by comparing their clinical features and inflammatory biomarkers to those of non-OCS-dependent subjects. The UBIOPRED cohort consisted of 372 severe asthma patients, with 44% classified as OCS-dependent. There was a similar female preponderance and BMI in both groups, but the OCS-dependent group had greater exacerbation rate (3/year versus 2/year; $p=0.001$), prevalence of nasal polyps (48% versus 23%; $p=0.0003$, higher GINA severity score ($p=0.01$), and greater use of nebulised bronchodilators and theophylline ($p<0.0001$, both). They also had lower pre-bronchodilator FEV1 (63.1% versus 66.4%; $p<0.05$). In induced sputum, eosinophils were non-significantly increased (5.2% versus 2.0%; $p=0.063$), but sputum macrophages were lower (13.9% versus 27.8%; $p=0.01$). There was an increase in the mixed granulocytic profile in sputum (26 versus 8%) and a reduction in the paucigranulocytic profile (10% versus 31%) (Chi-square $p<0.01$). In blood, neutrophil counts were higher while eosinophils were lower, indicating a systemic effect of OCS. FENO was higher (30 versus 22 ppb; $p=0.001$).

This preliminary analysis indicates that OCS-dependent severe asthma represents a more severe group with higher inflammatory biomarkers with lesser sensitivity to CS beneficial effects, characterised by an eosinophilic and neutrophilic sputum profile. Further *-omics* analysis in progress will provide a more precise delineation of this phenotype.

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Outcomes

The ultimate outcome of the project is to advance the understanding of asthma and create a handprint of severe asthma. To achieve these goals a number of other outcomes are being achieved.

These outcomes are to:

1. Generate consensus and global standard operating procedures (SOPs) that can be used in future asthma clinical trials
2. Create adult/paediatric groups of patients and collect and store their samples in biobanks
3. Analyse and compare symptoms and biomarkers from people with severe asthma and people without asthma
4. Identify phenotypes affecting exacerbations, normal asthma and disease progression
5. Generate phenotype "handprints"
6. Validate the phenotype "handprints" by checking their accuracy
7. Refine the phenotype "handprints" with pre-clinical and human exacerbation models
8. Establish if the 'handprints' can predict responsiveness to treatments in two studies, proving the validity of the concept, and in studies evaluating new or existing drugs. These handprint trials will be compared against the current 'best' treatment
9. Refine diagnostic criteria and phenotypes in asthma
10. Establish a platform for exchange, education and dissemination of the projects results, resources and lessons learnt

For updates on the project

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