The International Serious Adverse Events Consortium

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The International Serious Adverse Events Consortium is generating novel insights into the genetics and biology of drug-induced serious adverse events, and thereby improving pharmaceutical product development and decision-making.

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The impetus for the International Serious Adverse Events Consortium (iSAEC) arose from a series of interviews in 2006 with senior research and development leaders of major pharmaceutical companies, exploring how to build on the success of the SNP Consortium[1] to identify additional, high-value genomic research areas in which to apply this highly effective cross-industry collaborative model. The interviewees assigned the highest priority to exploring the genetic basis of drug-induced, rare serious adverse events (SAEs). In May 2006, with staff at the US Food and Drug Administration (FDA), we conceptualized the structure for a private, international research consortium to explore the genetic contribution to drug-induced SAEs. It was felt the opportunities for applying genomic technologies to better understand this vital aspect of drug safety would benefit both drug development and regulatory oversight. Equally significant were the complexity, logistics, management, risks, and cost associated with such a research initiative. No single institution possessed the resources, sufficient well-phenotyped cases, genomics expertise and international breadth to execute such a research endeavour alone. The stage was set for the development and launch of the iSAEC.

Scientific focus and organizational structure

The iSAEC is a pharmaceutical-industry-led and FDA-supported international research consortium, focused on identifying and validating DNA variants predictive of the risk of drug-induced SAEs. It was launched in 2007 with the scientific and financial support of six funding members (Abbott, GlaxoSmithKline, Johnson & Johnson, Pfizer, Roche and Sanofi-Aventis). Additional dues-paying members were added (Novartis, Takeda, Daiichi Sankyo, and The Wellcome Trust) as the consortium completed its Phase 1 research programme (focused on the genetics of drug-induced liver injury (DILI) and serious skin injury (DISI)). A separate call for funding and membership roster was developed for the Phase 2 research programme, which included ten dues-paying members (Abbott, GlaxoSmithKline, Pfizer, Takeda, Daiichi Sankyo, Novartis, Merck, Amgen, AstraZeneca and the Wellcome Trust), as well as three associate members that made in-kind, non-cash contributions to the research effort (Cerner, Clinical Data and Catholic Health Initiatives). The FDA has participated from the outset as an observer, advisor and research collaborator, but without formal membership status.

Since 2007, the iSAEC has collaborated with over 200 leading academic centres and scientists globally to:

- standardize and publish phenotype definitions for the major drug-induced SAEs (liver, skin, heart and renal injury);
- build diverse, well-phenotyped clinical cohorts and sample repositories for many of the major SAEs;
- apply optimal genomic and computational methods (including imputation) for effective genome-wide single nucleotide polymorphism (SNP) genotyping and exome sequencing;
- ensure timely public availability of scientific results/associated data (within 12 months after genotyping, regardless of publication timing) to the scientific community at no cost[2] (see Further information); and
- ensure the open use of all iSAEC data, unencumbered by intellectual property constraints[3].

The iSAEC's organization is virtual and composed of multiple collaborative teams, staffed by member volunteers and research collaborators, and under the direction of the iSAEC's CEO/Chairman. The iSAEC is governed by a board of directors (BOD) that consists of one director from each sponsoring member and the CEO, *ex officio*, and makes its decisions using a 'majority rules' model. The board delegates the oversight and management of the consortium's research agenda to the scientific management committee (SMC), which has representatives from each member company as well as scientific and clinical experts from many of its major collaborations. The SMC is supported by the Data Analysis and Coordination Center (DACC) at Columbia University as well as a network of genotyping and sequencing partners. The DACC coordinates the aggregation, quality control, analysis and release of all research data; prior to public data release, no

consortium member or collaborator may use the data for any purpose other than the advancement of the consortium's research (that is, there is no preferential access; see Further information for details of the data release policy).

Current status and scientific output so far

Over the past 7 years, the iSAEC has developed novel, international clinical networks to aggregate well-phenotyped case collections associated with specific SAEs and causal drugs. Specifically, we have aggregated subjects with DILI, DISI, drug-induced hypersensitivity syndrome (DIHSS), drug-induced renal injury (DIRI), drug-induced Torsades de pointes/prolonged QT effects (DITdP), inflammatory bowel disease (IBD) therapy-related SAEs such as pancreatitis and leukopenia, excessive weight gain (EWG) associated with class 2 antipsychotics, and osteonecrosis of the jaw (ONJ). Case enrolment has been completed for all SAEs, with the exception of DIRI and those related to IBD (see Supplementary information S1 (table)). By the end of 2015, the consortium expects to have aggregated close to 7,500 SAE cases spanning these phenotypes. The majority of this collection will be Caucasian, but it will contain important African, Indian and Chinese cohorts. The scale, depth, quality, and diversity of this recruitment effort are unprecedented in the history of drug safety research.

The iSAEC has or will conduct genome-wide genotyping of all collected subjects. In Phase 1, initial genome-wide association studies were conducted for DILI, DISI and DITdP, leading to several novel findings and key insights into the primary immune-related mechanisms underlying many of these SAEs (see Supplementary information S2 (box) for a list of publications). Following the success of the first phase, the BOD approved a plan to increase the existing DILI and DISI case collections, expand into DIHSS, DIRI, EWG, ONJ and IBD-related SAEs, expand investigations for selected SAEs into non-European populations, and explore the role of rare variants in SAEs with pilot exome sequencing studies for co-amoxiclav-induced liver injury, clozapine-induced agranulocytosis and DITdP.

To date, the iSAEC has completed 18 public releases of anonymized subject-level clinical and genotyping data, associated with 3,623 of its cases and controls. A total of 135 researchers and institutions have applied for and been granted access to the iSAEC database (see Further information). Through this open access policy, we hope to stimulate further analysis that will yield additional scientific insights and publications as collections and genetic analysis methods evolve[2].

The iSAEC is helping to set the precedent for genetic analysis of drug-induced SAEs and beginning to broaden the scientific understanding of these highly personalized reactions to otherwise safe and effective drugs. Through our research, we have demonstrated that the primary genetic contribution to SAE risk is through human leukocyte antigen (HLA) variation and the adaptive immune response, and that the variants with clinically meaningful effects can be detected in relatively small sample sizes (<50 cases in several instances). This bodes well for the feasibility of applying genomic methods in the future when an immunologically mediated toxicity is suspected. In those studies where we have performed sequencing analysis, our quest to identify rare variants (that is, <1% of the population) with a large SAE influence has, to date, been unfruitful. We remain uncertain as to the effects such rare genetic variants may have on SAEs. To date, most of our findings are drug-specific versus across multiple drugs, which may be expected given the important role for the major histocompatibility complex genomic region in the pathology of immunologically mediated SAEs and the very specific relationships observed between HLA alleles and clinical disease (for example, HLA-B*27 in ankylosing spondylitis and HLA-C*06 in psoriasis). Finally, there are a number of HLA alleles that are associated with different SAEs and for different drugs, including HLA-B*57:01, HLA-DRB1*07:01, and HLA-DRB1*15:01, that may provide important insights into the underlying biology of SAEs and offer strategies to predict or mitigate future SAEs.

Lessons learned and conclusions

Lessons learned in developing the iSAEC include:

- a clear, unifying, highly important mission is a must from the outset;
- to maximize membership and ease of formation, ensure the proposed effort is precompetitive and in the public good;
- develop the operating plan and uniform membership requirements with the potential funding members;
- have a high-quality, phased scientific/operating plan before recruiting funding members;
- establish dedicated, high-quality management early;
- develop funding requirements early, and work with the potential members on trade-offs to produce an affordable and effectively phased consortium;
- organize a board and well-defined committees with high-quality, dedicated leaders;
- outsource to the best external advisors/investigators via performance-based contracts;
- exceed expectations;
- make it fun and say "thank you" in meaningful ways;
- know when to terminate the consortium — begin with the end in mind!

Drug-related biomedical research options are exploding in number, complexity, risk and cost. To address the challenges, all stakeholders must work together to develop new collaborative research frameworks and diversified funding models that enhance financial leverage and research productivity. The iSAEC serves as an excellent example of such innovation.

1. Holden, A. L. The SNP consortium: summary of a private consortium effort to develop an applied map of the human genome. *Biotechniques* **32**, S22–S24 (2002).
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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
iSAEC Data Access Site: https://dataportal.saeconsortium.org/
iSAEC Public Data Access Policy: http://www.saeconsortium.org/?q=node/27

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (box)
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