

ISICR Standards Committee

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ISICR Standards Committee

- Established two decades ago to make recommendations regarding interferon and cytokine standards and standardization to the ISICR membership, and thereby to the international cytokine scientific community,
- The Committee works closely with the WHO, NIBSC, NIH, BEI Resources, pharmaceutical manufacturers, and regulatory agencies. The Committee includes members from several of these organizations.
- Current topics under discussion by the Committee include the establishment of appropriate standards for biosimilars, pegylated biopharmaceuticals, and antibodies directed against protein-based drugs.

ISICR Standards Committee: Members

- Ana Costa-Pereira, Imperial College, London,
- Evert Lamme, Merck-Serono, Geneva
- Amy Rossenberg, FDA, Bethesda, MD
- Huub. Schellekens, University of Utrecht,
- Martin Schiestl, Sandoz, Kundl
- Steve Swanson, Amgen Inc, Thousand Oaks, CA
- Meena Subramanyam, Biogen Idec, Cambridge, MA
- Robin Thorpe, NIBSC, Potters Bar, UK
- Michael Tovey (Chairperson), ENS, Paris, France

ISICR Standards Committee

- The Committee reports to and solicits input from the ISICR membership on the occasion of the annual joint meeting of the ISICR & ICS, a meeting that brings together more than 700 of the worlds leading scientists in the field of cytokine research.
- Committee reports and recommendations are published annually in the JICR newsletter and periodically in the JICR.
- Committee recommendations are also published periodically in other leading journals in the field.

**ISICR Standards Committee
Meeting Report**

Meeting: ISICR/Standards Committee
Date of minutes: October 3, 2010
Location: Chicago IL. USA

The meeting was called to order on Sunday, October 3, 2010.
The following topics were discussed :

1. - New Cytokine Reference Preparations

Robin Thorpe, NIBSC, UK, submitted a report on new cytokine reference preparations.

- Replacement standards

- G-CSF 2nd IS (Study completed; 13 labs from 9 countries)

replacement standard proposed (WHO ECBS – Oct'10)

- IL-2, GM-CSF, IL-8 (will require replacements within 2-3 years)

2. New standards

- TGF-beta3 (2 candidate preparations lyophilised)
–Collaborative study launch Oct'10, 7 participants, more needed
- IL-29 (2 candidate preparations lyophilised – not pegylated),
–Collaborative study to commence, participants needed
- IL-23 (1 candidate lyophilised, development of NIBSC ref reagent)
- BLYS (1 candidate lyophilised, development of NIBSC ref reagent)

3. Standards in development

- Donations & Collaborations required
- Provision of Novel cytokines
– IL-21, IL-27 etc
- Provision of cytokines for replacement standards
–GM-CSF, IL-8
- Provision of Growth factors
– Placental growth Factor, soluble VEGFR1

- Participation in Collaborative Studies
- TGF-beta3 (Oct 2010) & IL-29 (January 2011), BLYS

Those interested in participating in the studies outlined above please contact :
Meenu.Wadhwa@nibsc.hpa.org.uk

II. - Initiatives to promote the use of cytokine standards

The Committee discussed initiatives to promote the use of cytokine standards including the recent publication in the journals Cytokine, JICR, and JLB of an editorial outlining the role of the ISICR Standards Committee, the WHO, and the NIBSC in the establishment of international cytokine standards and reference preparations together with a list of reagents available from the NIBSC.

III. - Reference Preparations for Human Anti-drug Antibodies

Patients treated with cytokines such as interferon-beta or growth factors such as erythropoietin may produce antibodies against the product that can adversely affect the efficacy of treatment. There is a need to standardize immunogenicity data obtained in different clinical studies using different drugs and different assays.

Two initiatives have been undertaken :

- The establishment of a standardized neutralizing antibody assay for detection of antibodies against IFN-beta (EMA/CHMP/BWP/580136).
- The establishment of an antibody reference panel for the standardization of EPO antibody assays (WHO – ECBS proposal, Oct 2010). In addition a panel of human antibodies of different characteristics (isotypes, affinities) for use as performance indicators for different EPO antibody assays is currently being established.

IV. - Other Business

Co-ordination of the Committee's initiatives with other bodies such as World Health Organization (WHO), the National Institute for Biological Standards and Control (NIBSC), the U.S. National Institutes of Health (NIH), the Biodefense and Emerging Infections Resources Repository (BEI Resources), pharmaceutical manufacturers, and regulatory agencies (FDA, EMA, JPMDA) was also discussed.

Respectfully submitted,
Michael Tovey
Chair, ISICR Standards Committee

Promotion of the Use of International Cytokine Standards & Reference Preparations for Experimental & Clinical Investigations

- *J. Interferon & Cytokine Res.* **30**:639-641, 2010
- *Cytokine*, **52**:2-3, 2010
- *J. Leukocyte Biology*, **88**:425-426, 2010

WHO International Cytokine Standards and Reference Preparations

The ability to quantify the activity of cytokines is an essential part of experimental and clinical investigation and is to a large extent dependent upon the availability of suitable cytokine standards and reference reagents. The ISICR Standards Committee was established two decades ago to make recommendations regarding interferon and cytokine standards and standardization to the ISICR membership, and thereby to the international cytokine scientific community. The Committee works closely with the World Health Organization (WHO), the National Institute for Biological Standards and Control (NIBSC), the U.S. National Institutes of Health (NIH), the Biodefense and Emerging Infections Resources Repository (BEI Resources), pharmaceutical manufacturers, and regulatory agencies. The Committee includes members from several of these organizations. Current topics under analysis by the Committee include the establishment of appropriate standards for biosimilars, pegylated biopharmaceuticals, and antibodies directed against protein-based drugs. The role that the Committee plays as a source of information and recommendations to the ISICR membership, and to the international cytokine scientific community as a whole, is very much dependent upon suitable standards and reference materials being made available by the NIBSC. Similarly, the Standardization and Nomenclature Committee of the ICS reviews the need for cytokine standards and their usage.

The accompanying table lists cytokine and growth factor preparations available from the NIBSC. International Standards and Reference Reagents are established by the Expert Committee on Biological Standardization of the WHO.

The use of these International Standards and Reference Reagents to calibrate commercially available or laboratory made reagents will facilitate comparisons of data between assays, different laboratories, and individual studies.

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Control,

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A wide range of WHO International Biological Standards and reference materials are available for the calibration of assays.

Human Cytokine Standards and Reference Reagents

Preparation ¹	Product Code	Status ²
Interleukin 1 alpha	86/632	IS
Interleukin 1 beta	86/680	IS
Interleukin 2 cell line derived	86/504	IS
Interleukin 2	86/564	RR
Interleukin 3	91/510	IS
Interleukin 4	88/656	IS
Interleukin 5	90/586	WRR
Interleukin 6	89/548	IS
Interleukin 7	90/530	WRR
Interleukin 8	89/520	IS
Interleukin 9	91/678	WRR
Interleukin 10	93/722	WRR
Interleukin 11	92/788	WRR
Interleukin 12	95/544	WRR
Interleukin 13	94/622	WRR
Interleukin 15	95/554	WRR
Interleukin 17	01/420	WRR
Interleukin 18	03/200	WRR
M-CSF	89/512	IS
G-CSF	88/502	IS
GM-CSF	88/646	IS
Leukemia inhibitory factor	93/562	WRR
Oncostatin M	93/564	WRR
Stem cell factor	91/682	WRR
Flt 3 ligand	96/532	WRR
Bone morphogenetic protein-2	93/574	WRR
RANTES	92/520	RR
MCP-1	92/794	RR
GRO-alpha	92/722	RR
IFN alpha leukocyte	94/784	1 st IS
IFN alpha 1(D)	83/514	1 st IS
IFN alpha 1/8	95/572	1 st IS
IFN alpha 2a	95/650	2 nd IS
IFN alpha 2b	95/566	2 nd IS
IFN alpha 2c	95/580	1 st IS
IFN alpha n1 lymphoblastoid	95/568	2 nd IS
IFN alpha n3 leukocyte	95/574	1 st IS
IFN alpha consensus	94/786	1 st IS
IFN omega	94/754	1 st IS
IFN beta	00/572	3 rd IS
IFN beta ser17	00/574	RR
IFN beta fibroblast	00/576	RR
IFN gamma	87/586	RR
IFN gamma leukocyte	82/587	BWS
TGF beta 1	89/514	RR
TGF beta 2	90/696	RR
TGF beta 3	98/608	RR
Thrombopoietin	03/124	RR
TNF alpha	88/786	2 nd IS
TNF beta	87/640	WRR
TRAIL	04/166	WRR

These materials are available from Standards Processing Division, NIBSC, Blanche Lane, South Mimms, Potters Bar, Herts EN6 3QG, UK, e-mail standards@nibsc.hpa.org.uk or Fax 01707641064. NIBSC does not charge for these materials, however there is a handling charge to cover the costs of administration, storage, and dispatch. The handling charge is currently £63 per ampoule. A comprehensive catalogue of reference materials is available from the above address or from the NIBSC website; www.nibsc.ac.uk.

Human Growth Factor Standards and Reference Reagents

Preparation ¹	Product Code	Status ²
Basic Fibroblast Growth Factor	90/712	IS
Brain-derived neurotrophic factor	96/534	WRR
Ciliary Neurotrophic Factor	94/684	WRR
Epidermal Growth Factor	91/530	IS
Epidermal Growth Factor (1-52)	91/550	WRR
Hepatocyte Growth Factor	96/564	WRR
Hepatocyte Growth Factor precursor	96/556	IS
Keratinocyte Growth Factor	03/150	WRR
Keratinocyte Growth Factor (24-163)	03/148	WRR
Leptin	97/594	IS
Nerve Growth Factor	93/556	WRR
Neurotrophin-3	98/718	RR
Platelet derived Growth factor BB	94/728	IS
Vascular Endothelial Growth Factor 165	02/286	WRR

Mouse Cytokine Reference Reagents

Preparation ¹	Product Code	Status ²
GM-CSF	91/658	RR
Interleukin 1-alpha	93/672	RR
Interleukin 1- beta	93/668	RR
Interleukin 2	93/566	RR
Interleukin 3	91/662	RR
Interleukin 4	91/656	RR
Interleukin 6	93/730	RR
Interleukin 7	93/740	RR
Interleukin 9	93/504	RR
Leptin	97/626	IS
TNF-alpha	88/532	RR

¹ - All preparations listed above are rDNA derived unless specified ;

² - IS - WHO International Standard; WRR - WHO Reference Reagent; RR - NIBSC Reference Reagent; BWS - British Working standard

Further Information

National Institute for Biological Standards and Control - Assuring the quality of biological medicines
Blanche Lane South Mimms Potters Bar Hertfordshire EN6 3QG United Kingdom
Tel +44 (0)1707 641000 Fax +44 (0)1707 641050 www.nibsc.ac.uk
A World Health Organization Laboratory for Biological Standards

Beta-interferons and neutralizing antibodies (in multiple sclerosis)

A Common Assay Methodology

Co-ordinator Huub Schellekens

EMEA/CHMP/BWP/580136

13 February 2008

Traditionally IFN Potency has been Determined
using the Cytopathic Effect Antiviral Assay

Viral Cytopathic Effect Assay

- Involves transcriptional activation of >150 genes
- Difficult to standardize
- High degree of assay variation
- Low selectivity: cannot distinguish IFN α , or IFN β , from IFN γ , or non-specific inhibition of virus
- Low sensitivity (serum matrix effects)
- Use of a pathogenic virus requires Biosafety BSL2 lab
- Requires titration of virus stocks
- Takes 3 to 4 days to complete
- Requires specialized personnel
- Difficult to transfer to CRO

EMA Common Assay Methodology

MxA – ELISA Assay

- MxA IFN-induced antiviral protein
- A549 cells treated with IFN beta enhanced expression of MxA
- A549 cells treated with a mixture of patient serum and challenge IFN overnight
- Cells lysed and amount of MxA protein quantified by ELISA
- MxA ELISA based upon a rat monoclonal antibody for capture & a biotinylated mouse Mab for detection
- Neutralizing titer calculated using the Kawade methodology (TRU/ml)

TNF α Antagonists and neutralizing antibodies

(Crohn's Disease & rheumatoid arthritis)

Proposed Common Assay Methodology

TNF α Antagonists and neutralizing antibodies

Proposed Common Assay Methodology

- A common assay for TNF- α antagonists would allow direct comparisons of the relative immunogenicity of different products.
- A common assay read-out for TNF- α antagonists would allow direct comparisons of relative immunogenicity of innovator molecules and biosimilars.
- Ideally the assay should allow simultaneous quantification of drug activity and anti-drug NAbs
- The assay should be able to distinguish between NAbs to different TNF- α antagonists

ISICR Standards Committee:

The Future

- The Committee has played a significant role in the establishment of international cytokine standards a number of which have served as reference standards for therapeutic proteins.
- The Committee would welcome a closer collaboration with other bodies involved in the establishment of reference standards for therapeutic proteins