IgA nephropathy (IgAN), the most common glomerular disease worldwide, is potentially progressive to renal failure. In individual patients its course is unpredictable before development of severe proteinuria, hypertension, reduced glomerular filtration rate and renal fibrosis. There is a need to detect progressive cases in early stages, when a therapeutic intervention is more likely to be effective.

A breakthrough report just published from an International Consensus - based on a retrospective analysis of 265 adults and children with IgAN from four continents - focuses on prognostic information provided by renal biopsy. According to this Oxford Classification of IgAN, four pathological features (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) predict renal outcome independently from all clinical indicators at the time of biopsy and during follow up (Kidney International 2009;76:534-45; and Kidney International 2009;76:546-56). The limited number of patients and their heterogeneous origin indicate a need for validation studies involving large cohorts of patients. The proposed study will investigate European patients and the results will be complementary to those from similar studies in North America and Asia, allowing a global perspective on the value of these predictive factors.

Biopsy-proven IgAN with long follow-up or rapidly progressive course (about 500 cases) will be enrolled by 26 Centers of Nephrology and Renal Pathology from 9 Countries. Renal biopsies will be scored by the local pathologist and centrally reviewed in Oxford. Clinical data at renal biopsy and during the follow-up will be provided by local Nephrologists to the Coordinating Center. Statistical analysis will be performed by Canadian experts.

This multicenter, multinational study supported by the ERA-EDTA Working Group of Immunonephrology will provide information beyond the validation of the Oxford classification of IgAN, aiming at detecting for each lesion the most effective treatment and the “point of no return” when no treatment is effective.

5 Key words: 1) glomerular diseases 2) IgA nephropathy 3) risk factors for progression 4) renal pathology 5) chronic kidney disease
**Relevance in Europe**

1) The relevance for Europe is because IgAN is a common cause of CKD, progressing to need of renal replacement treatment. It is the most dominant glomerular disease in Europe, accounting for 20-30% of renal biopsies and representing half of all cases of glomerulonephritis. The 20-year cumulative renal surviving rate ranges from 14 to 39%. Its progression to end-stage renal disease occurs over a wide time range from a few months to more than 50 years. Hence, IgAN is likely to be underdiagnosed particularly in elderly patients with hypertension found to have CKD of unknown origin. The ERA-EDTA registry reported in 1991 that 67% of patients with IgAN enter a chronic dialysis program as young adults (24-54 year-old). Knowing the slow function decline in IgAN, it is likely that many of these progressive cases began in childhood. Thus a broad spectrum of patients are affected by this disease and therefore the study has a potential of benefit in all age groups by its focus on detecting new risk factors for progression.

2) The study proposed will place European nephrologists and renal pathologists in a worldwide network of scientists, supplementing/augmenting similar validation studies ongoing in other continents, including North America and Asia. This proposal will also provide updated information for European patients.

3) This study will provide a template for collaboration among European nephrologists and renal pathologists in methodology related to scoring renal biopsies, collecting clinical data and participating in data analysis (in collaboration with experts from Canada familiar with the methodology used in the original Oxford classification).

4) This study, proposed by the newly formed ERA-EDTA Working Group of Immunonephrology, will provide added value by establishing a European infrastructure network of nephrologists and pathologists which can act as a nidus for future Europe-wide investigations on glomerular and immunological renal disorders.

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PROPOSED RESEARCH

1. Purpose.

IgA nephropathy (IgAN), the most common glomerular disease worldwide, and progresses to end stage renal disease in about 20% of cases by 10 years. Its clinical course is unpredictable before development of severe proteinuria, hypertension, reduced glomerular filtration rate and extensive interstitial fibrosis. There has been continuing debate whether pathological features seen on renal biopsy contribute additional prognostic information particularly in early stages, when a therapeutic intervention is more likely to be effective.

A breakthrough report just published from an International Consensus - based on a retrospective analysis of 265 adults and children with IgAN from four continents - focuses on prognostic information provided by renal biopsy. According to this Oxford Classification of IgAN, four pathological features (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) predict renal outcome independently from all clinical indicators at the time of biopsy and during follow up (Kidney International 2009;76:534-45; and Kidney International 2009;76: 546-56).

Since that work was done on a limited number of patients of rather heterogeneous origin, there is a need for validation studies which are now being planned in North America, Asia, and Europe.

The purposes of this European study are:

1) to validate the Oxford Classification of IgAN in an European cohort from a multinational network of nephrology and renal pathology centers which will provide biopsy material and clinical data of patients encompassing all clinical and histological features of IgAN,
2) to further improve the pathology classification detecting the value of selected associations of readily identified pathology lesions and clinical features, aiming at detecting the most effective treatment and the “point of no return” when no treatment is effective.
3) to improve the research network among European Countries collaborating with a Canadian center performing the necessary statistics, meanwhile establishing connections with complementary studies in North America and Asia, in a global research team.

2. Background.

IgA nephropathy [IgAN], the most common glomerular disease worldwide, progresses to ESRD in approximately 20% of cases within 10 years (1-3). Its course is not easily predicted using clinical data until advanced disease is confirmed by the development of severe proteinuria, hypertension and reduced GFR (1-6). Recent work has confirmed the prognostic importance of reduction in proteinuria during follow up, allowing increasing refinement of the prognostic information (7). Pathologists have produced several classifications of IgAN over the last 25 years (8-15), each has strengths and
limitations in predicting prognosis, and none has gained pre-eminence. There has been continuing
debate whether pathological features seen on renal biopsy contribute additional prognostic information
beyond that provided by clinical features (16). This lack of consensus on classifications based on
pathology has curtailed and weakened the investigation of this disease.

An international consensus involving nephrologists and pathologists from many parts of the
world, from 8 countries and 4 continents, has been established (17) and has developed a new
classification for IgAN, called the Oxford Classification, (18,19). This classification is based on
detailed analysis of retrospective clinical data obtained on 265 adults and children with IgAN, followed
for a median of 5 years in concert with intense detailed review of their renal biopsy tissue (Pathology
definitions are detailed in Appendix 1).

Six pathology variables were identified on the basis of reproducibility among pathologists, least
susceptibility to sampling error, and ease of scoring in routine practice while avoiding strong
colinearity (mesangial hypercellularity score, segmental glomerulosclerosis or adhesion, endocapillary
hypercellularity, cellular or fibrocellular crescents, tubular atrophy/interstitial fibrosis, artery score.
Four of them (mesangial hypercellularity score, segmental glomerulosclerosis or adhesion,
endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) were shown to have
independent value in predicting renal outcome even after taking into account all clinical indicators
available at the time of biopsy as well as during follow up (Table 1). The value of crescents could not
be addressed due to their low prevalence in the enrolled cohort which did not include rapidly
progressive cases.

The Oxford classification of IgAN needs validation, and studies are being planned in North
America, Asia, and Europe. The observational study proposed will provide validation of the Oxford
Classification in a European cohort, as well as testing extension of the classification, for example to
those with more severe, rapidly progressive IgAN.

We seek ERA-EDTA support for this study involving several countries across Europe. It will
necessitate European nephrologists and renal pathologists to work together for scoring renal biopsies,
for collecting clinical data as well as participating in the analysis in collaboration with the experts
from Canada familiar with the methodology used in the original Oxford classification.

This study is proposed by the newly formed ERA-EDTA Working Group of Immunonephrology.
As well as the immediate benefits of the IgAN study, this proposal will also provide added value by
establishing a European infrastructure network of nephrologists and pathologists which can act as a
nidus for future Europe-wide investigations on glomerular and immunological renal disorders.
3. Plan of investigation including research group strategy

26 Centers of Nephrology and Renal Pathology from 9 European Countries (Spain, France, United Kingdom, Italy, Germany, Sweden, Poland, Netherlands, Turkey) have agreed upon providing clinical data and renal biopsy material available for the reviewing process according to the Oxford Classification for IgAN (18, 19). Each Center will contribute 10-30 cases.

Selection of patient cohorts for testing

Inclusion criteria. Patients with biopsy-proven IgAN (defined by standard criteria, including predominant or codominant mesangial deposition of IgA, see Appendix 1 for histology definition), both children and adults, will be included regardless of treatment given. They must have a renal biopsy available for reviewing which include 8 or more glomeruli, and at least 3 measurements of creatinine, proteinuria and blood pressure, the first of which should be within 3 months of the date of renal biopsy and the last at the end of the follow-up. Patients must accomplish the following criteria:

1) having progressed to ESRD regardless of the duration of follow-up
2) have a follow-up longer than 1 year.

Patients with significant deterioration in estimated GFR (eGFR) (i.e. showing at the end of follow-up 50% reduction in renal function) and those with long follow-up (> 5 years) will be preferentially included to maximise the opportunity to identify discriminatory pathological variables of independent importance in predicting outcome.

Patients who have received antihypertensive or immunosuppressive medication will be included as well.

Exclusion criteria. Patients with renal biopsies including <8 glomeruli. Secondary IgAN such as Henoch-Schönlein nephritis, and IgAN with comorbid conditions such as diabetes.

Pathology definitions

A score sheet will be completed by individual pathologists for each biopsy using the instructions (Table 2, IgAN validation score sheet, Appendix 1, Pathology definitions).

Continuous variables will be studied as categorical according to the Oxford Classification (18,19), hence the cut-off used for the mesangial hypercellularity score will be 0.5 (equivalent to 50% of glomeruli showing mild mesangial hypercellularity); segmental glomerulosclerosis, endocapillary hypercellularity and extracapillary proliferation will be categorized as either present or absent; tubular atrophy/interstitial fibrosis and arterial lesions will be categorized as absent/mild (0-25%), moderate (26-50%) or severe(>50%).
Clinical dataset

Clinical data sheets will be completed by nephrologists (table 3 and 4). Demographics will include date of birth, gender, ethnicity, date of biopsy. Children will be considered subjects aged <18 years at biopsy. Clinical parameters collected within 3 months of date of biopsy and during follow up include: systolic and diastolic blood pressure (BP), weight, height, serum creatinine and 24hr urine protein or urine protein:creatinine ratio. In order to provide consistency between measurements in adults and children, proteinuria will be expressed in g/24hr /1.73m² in children and g/24 hr in adults. Treatment modalities will be recorded. Collected data will be verified by a data manager.

Clinical data definition

GFR will be estimated using the 4 variable MDRD formula in adults (21) and the Schwartz formula in children (22). ESRD is defined as eGFR <15 ml/min/1.73m². Mean arterial pressure (MAP) is diastolic BP +1/3 pulse pressure. In children standard deviation score for MAP will be calculated [20] and used to normalize MAP to adult values. For each patient, an yearly average MAP and proteinuria will be determined.

Statistical methods

No available data could inform a calculation of the necessary number of cases to allow confident exclusion of type 1 statistical errors in subsequent analyses. A pragmatic recruitment goal has been set at 500 cases comprising 425 adults and 75 children.

Normally distributed variables will be expressed as mean ± standard deviation and compared using student’s t-test, one-way ANOVA or Pearson test. Non-parametric variables will be expressed as median and range and compared using either Mann-Whitney, Kruskal-Wallis or Spearman test. Categorical variables will be expressed in percentages and compared using Pearson Chi-Square test.

Continuous pathological variables will be categorized to facilitate the applicability of the classification. The relationship between continuous pathological variables and the rate of renal function decline (dichotomized in 2 groups using the median value) will be depicted with receiver operating characteristic (ROC curves) and the optimal cut off predicting a worse outcome will be determined from these.

Three clinical outcomes will be studied to address the predictive value of pathology variables: [a] the rate of renal function decline (slope of eGFR); [b] survival from a 50% reduction in renal function, or ESRD; [c] proteinuria during follow up [as a surrogate outcome measure]. The rate of renal function decline will be determined by fitting a straight line through available data for eGFR using the
principle of least squares.

Univariate followed by multiple linear regression will be used to determine independent predictors of slope and follow-up proteinuria. Different relevant multivariate models will be tested. Only pathology variables significantly associated with outcome will be further considered. Slope will also be categorized into two halves to derive odds ratios of a more rapid rate of renal function decline using logistic regression. Survival analysis using Cox regression will be performed to test the association between each pathological finding and a combined event (50% reduction in renal function or ESRD, to increase the rate of events and permit a valid multivariate analysis). The same models described above will be studied through multivariate Cox regression. Interactions with age, ethnicity and immunosuppressive treatment will be investigated. All p values will be two-tailed and values less than 0.05 will be considered statistically significant. Confidence intervals (CI) will include 95% of predicted values.

Reproducibility for each pathology variable of all biopsies which will be reviewed by the central Pathology experts, will be assessed using intraclass correlation coefficient (ICC) (23) which was adopted for the work leading to Oxford classification (19). Validation will be performed by applying coefficients obtained from multivariate analyses of the Oxford trial to the new cohort. Using the previously reported coefficients with the new dataset, we will be able to calculate a predicted rate of renal function decline (linear), the probability of have a more rapid rate of renal function decline (logistic) or the hazard ration of having a 50% reduction of renal function or ESRD (Cox). These predicted outcomes of the validation cohort will be compared to the actual outcomes observed. Analyses will be carried out using SPSS software (version 11, SPSS Inc. Chicago IL).

Research Group strategy

The following groups will be involved in the research:

- The coordinating center: Coppo R, Turin, Italy (Applicant for the project), Camilla R, Turin Italy, assistant to coordination

- Steering committee group: Coppo R, Feehally J, Roberts I, Cook T, Cattran D, Troyanov S (core group of the Oxford classification)

- Pathology review center: Roberts I (Oxford, UK)

- Statistical analysis center: Troyanov S, Cattran D (Montreal and Toronto, Canada)

- 26 Clinical Nephrology and Renal Pathology centers
Phase I: Patients enrolment

Clinical nephrology centers
- List of patients with IgA nephropathy meeting the enrolment criteria
- List sent to renal pathology centers

Renal pathology centers
- Check availability of renal biopsy material for review

LIST OF ENROLLED CASES SENT TO COORDINATING CENTER

Phase II: Clinical data collection and renal biopsy scoring

Clinical nephrology centers
- Clinical data spreadsheet filled-in

SPREADSHEETS SENT TO COORDINATING CENTER

Renal pathology centers
- Renal biopsies scored by the local pathologists blinded to the clinical data
- Already scored biopsies sent to the pathology review center

Pathology review center
- Renal biopsy slides reviewed, blinded to clinical data and local scoring

SPREADSHEETS SENT TO COORDINATING CENTER
Plan of the study

**Phase I: Patients enrolment.**

Each Nephrology and Pathology Center will

- meet the requirements of institutional review boards and ethics committees to allow the circulation of 1 de-identified PAS-stained renal biopsy specimen and clinical data within and beyond its country of origin.
- complete de-identified clinical data sheet (Tables 3 and 4) for eligible patients which are returned to the Coordinating Center (Turin, Italy)

The Coordinating Center will
- ensure clinical data completeness, communicating with each Center as necessary.

**Phase II: Clinical data collection and renal biopsy scoring**

- Each renal biopsy will be scored by the local pathologist blinded to the clinical data according to the detailed instructions (Appendix 1) and the pathology sheet (Table 2) will be filled and sent to the Study Coordinating Center.
- Each pathology Center will send the slides already scored to Oxford for a central re-scoring. In exceptional cases of impossibility to move slides, an on
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site visit from a pathologist of the Oxford team will be organized.
• The second pathology report will be sent to the Study Coordinating Center.

**Phase III: Renal biopsy review**

• The Pathology Review Center, blinded to clinical data and to the scores given by local pathologists, will score all renal biopsies and send the results to the Study Coordinating Center.

**Phase IV: Data collection**

• Collected data will be verified by a data manager in the Coordinating Center, which will ensure clinical data completeness, communicating with each Center as necessary.

**Phase V: Statistical analysis and publication**

• Statistical analysis will be performed by the Statistical Analysis Center (Canada).
• Data analysis will be overseen by the steering committee (core group of the Oxford classification: Coppo R, Feehally J, Roberts I, Cook T, Cattran D, Troyanov S).

### 4. Indication of timescale and milestones to be achieved

**Timescale of the study**

Database and pathology forms are available
- Months 0-3. Nephrologists: each Center will review the records of patients with diagnosis of IgAN meeting the selection criteria and will fulfil all requirements of institutional review boards and ethics committees to allow the circulation of anonymised pathological material and clinical data within and beyond its country of origin.
- Months 3-6. Pathologists: each renal biopsy will be scored by one local pathologist blinded to the clinical data according to the detailed instructions (Table 2 and Appendix 1) and the histology sheets will be filled
- Months 3-6. Nephrologists: clinical data from individual patients will be included filling data sheets (Tables 3 and 4)
- Months 6-12: Each biopsy will be reviewed by the pathologists team in Oxford either by slide
circulation or by on-site visits. Both original and reviewed pathology reports will be sent to the Study Coordinating Center.

- Months 3-12 The data sheets will be collected by the Study Coordinating Center (Turin), which will thoroughly check the database completeness
- Months 12-16 Statistical analysis will be performed by the Statistical Analysis Center (S. Troyanov, Canada).
- Months 15-18 Data will be discussed within the steering committee, then draft results will be circulated among all the participating Centers. Final report will be completed and a manuscript submitted.

Milestones to be achieved

This multicenter collaborative study has several relevant milestones:

1) To establish working principles for the ERA-EDTA working group of “Immunonephrology” with a high quality multicenter study, which offers the opportunity to implement the newly created network.

2) To involve ERA-EDTA in this Collaborative International Consensus group (as far as Europe in concerned) initiated under the auspices of the International Society of Nephrology, the Renal Pathology Society and the International IgAN Network.

3) To test the reproducibility of the new Oxford classification for IgAN in different European Centers, aiming at facilitating an improvement in data exchange

4) To validate the Oxford classification on a large European cohort encompassing all ages and different clinical and pathological features, aiming at facilitating networking of Centers.

This process will finally lead to other relevant milestones:

1) It will accelerate progress in developing a prognostic system with the sensitivity and specificity to predict outcome for individual patients.

2) It will increase the capacity to make international comparisons between different outcome studies,

3) It will enhance new opportunities to refine the stratification of risk for progression

4) It will eventually allow the design of more informative clinical intervention trials. A slowly progressive disease like IgAN needs large studies of long duration to evaluate new interventions unless patients with a high risk of progression can be better defined early in the course of the disease. The validation study on a large cohort of IgAN patients from various European countries will provide the suitable basis for this aim.

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**Person N. 1**

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**Major field of interest:**

The major field of interest of the applicant is IgA nephropathy (IgAN), either primary and secondary to Henoch-Schoenlein purpura.

The applicant focused particular interest in the following fields:
- Pathogenetical mechanisms operating in IgAN leading to renal damage and to disease progression.
- Aberrantly glycosylated IgA in circulation in patients with IgAN.
- Effect of desialylated/degalactosylated IgA on cultured mesangial cells.
- Abnormalities of immune system pathways in circulating lymphomonocytes of patients with IgAN.
- Risk factors for progression of IgAN. Histological feature of IgAN related to progression of IgAN.
- Therapy of IgAN: plasma exchange in rapidly progressive cases, treatment with ACE-inhibitors.
- Genetic and serological factors affecting recurrence of IgAN after transplantation.

The applicant has also been interested in other fields, particularly in:
- Clinical Nephrology: minimal change disease, focal segmental glomerulosclerosis, lupus nephritis, vasculitis, rare glomerular diseases, haemolytic uremic syndrome, acute renal failure, reflux nephropathy, pielonephritis,
- Chronic kidney diseases and renal replacement therapy: biocompatibility of hemodialysis and peritoneal dialysis,
- Clinical Transplantation in children
- Basic science research: immunoglobulins, immune complexes, mesangial, endothelial and peritoneal cell cultures.

- **Summarize the main outcomes of your research** work/programme(s) in the last 5 years (500 words maximum):

1) The applicant is Secretary of the International IgA nephropathy Network (www.igan-word.org) and member of the steering committee of the International Consensus of Nephrologists and Pathologists from Europe, America, Asia and Australia who developed the Oxford Clinico-pathological classification of IgAN (1,2)

2) The applicant coordinated a European multicenter randomized placebo controlled trial in patients with IgAN, a Concerted Action of Biomedicine and Health of the European Community (Biomed 2 PL96247). 23 European Centers from 5 Countries participated in this randomized trial (IgACE) investigating the effect of ACE-inhibition in children and young patients with proteinuric IgAN. Patients (9-35 years old) were randomized to Benazepril, 0.2 mg/Kg/day or placebo and were followed in median for 38 months. Results were published in JASN (3) The expertise in the field of IgAN is testified by the Authorship of Chapters on IgAN (e.g. 4,) and review articles (5,6)
3) The applicant succeeded in performing a Multicenter collaborative Italian Study in transplanted patients having had IgAN as renal disease leading to renal replacement treatment. Five Italian Centers participated in the study. Genetic factors, including genes encoding for cytokines and chemokynes as well as for the renin angiotensin system and serologic factors, including aberrantly glycosylated IgA and macromolecular IgA were detected and correlated with recurrence of IgAN in the grafted kidney. Results were published in Ref 7.

4) The applicant chaired a Multicenter collaborative Italian Study of the Immunopathology Group of the Italian Society of nephrology investigating the predictive value of clinical and histological features on the progression of IgAN secondary to Henoch-Shoenlein Purpura: 43 Italian Centers participated in the study Results were published in Ref 8. The expertise in the field is testified by the Authorship of Chapters on IgAN secondary to Henoch-Schoenlein Purpura (e.g.9)

5) The applicant participated in several research supported by the Italian National Health Ministry which investigated the presence of aberrantly glycostlated IgA in IgAN and some immune abnormalities of circulating lymphomonocytes in patients with IgAN, namely the switch from proteasome to immunoproteasome, which may favour the antigen presentation and the immune response (Chair A.Dal Canton, 2004; and Chair PA Tovo, 2005) Results were published in several papers, including Ref 10 and 11

References


References:  
Total number of peer reviewed publications in Pub Med: 206

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<td>BA</td>
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<td>Pathogenesis of IgA nephropathy - including studies of control of IgA production, IgA glycosylation and IgA receptors.</td>
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<td>Genetic susceptibility to IgA nephropathy [part of MRC/Kidney Research UK funded National DNA Bank for Glomerulonephritis].</td>
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<td>Classification of IgA nephropathy - convenor of international working group which has produced [2009] a new clinicopathological classification.</td>
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<td>Kidney disease in minority populations - including epidemiology of kidney disease in South Asians, and health services research investigating population awareness and access to care [collaboration with Imperial College &amp; University of Bedfordshire]</td>
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<td>Effects of exercise in chronic kidney disease - immunity, muscle metabolism, clinical outcomes [collaboration with Loughborough University]</td>
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**Summarize the main outcomes of your research work/ programme(s) in the last 5 years (500 words maximum):**

- I am the coordinator of the International IgA nephropathy Network (www. igan-word.org) and member of the steering committee of the International Consensus of Nephrologists and Pathologists from Europe, America, Asia and Australia who developed the Oxford Clinicopathological classification of IgAN (1,2). I created the platform for the collaborative work of many nephrologists and pathologists from all over the world and I succeeded in organizing the fruitful meetings in Oxford, which generated the new classification of IgAN.

- I am a leader researcher in the field of IgAN mostly focusing on biochemical abnormalities of circulating IgA. My group has performed several investigations on the origin of the cells producing aberrantly glycosylated IgA1. Moreover I am involved in genetic studies on the genetic background of IgAN.

- I have recently been appointed as president elect of the International Society of Nephrology.

- I was president of the British Association.

**References:**

Total number of peer reviewed publications in Pub Med: **187**
Publications (List up to 5 recent publications relevant to proposed project)


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Person N. 3

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<td>Ian Roberts</td>
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Place of Birth (Country): Zellingborough (UK)  
Present Nationality: UK  
Sex: Male  
Year Conferred  
1983  
1996

Degrees/Diplomas

- BA  
- FRCPath

Major field of interest:
Pathology of IgA nephropathy, and risk factors for progression.

Summarize the main outcomes of your research work/programme(s) in the last 5 years (500 words maximum):

I was responsible for designing and managing the study that led to the Oxford Classification of IgA nephropathy on which the present application is based.

References:
Total number of peer reviewed publications in Pub Med:
Publications (List up to 5 recent publications relevant to proposed project)


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**- Major field of interest:**

Renal Pathology

**- Summarize the main outcomes of your research work/ programme(s) in the last 5 years (500 words maximum):**

- My research is into pathological mechanisms in glomerulonephritis. I have studied animal models to elucidate genes that are associated with susceptibility to glomerulonephritis and have shown that in a strain of rat susceptible to crescentic glomerulonephritis there are seven genetic loci that control susceptibility. I have identified genes responsible for susceptibility at two of these loci.

- My clinical position is as a renal pathologist at the West London Renal and Transplant Centre. My research in human glomerulonephritis has centred on the classification of glomerulonephritis and reproducibility of the assessment of histological features. My work has particularly focused on SLE and IgA nephropathy. I was responsible for designing and managing the study that led to the Oxford Classification of IgA nephropathy on which the present application is based.

**References :**

Total number of peer reviewed publications in Pub Med: 133

**Publications (List up to 5 recent publications relevant to proposed project)**


4. Philibert D; Cattran D; Cook T. (Jan 2008). Clinicopathologic correlation in IgA nephropathy. SEMIN NEPHROL. 28:10-17


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<td>FRCPC (nephrol)</td>
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- **Major field of interest:**

Glomerulonephritis

- **Summarize the main outcomes of your research work/ programme(s) in the last 5 years (500 words maximum):**

My fields of interest included glomerular disease as well as biostatistics and clinical epidemiology. In the previous 5 years, my research work has addressed:

- The risk assessment of glomerular disease. In particular, with a focus on quantifying the predictive values of proteinuria and gender in primary glomerular disease and compared them to other known risk factors.
- I have studied the predictive value of inflammatory urine biomarkers in the progression of diabetic and non-diabetics glomerular disease. In particular, we have shown that urinary monocyte chemotactic protein 1 predicts the rate of renal function decline independently and additively to proteinuria.
- I have also studied the predictive value of pathology in membranous nephropathy.
- I participated in the completion of the “International Classification of IgA Nephropathy”. Specifically, I was responsible for the statistical analysis of the data collected.
- I leaded a study on the risk factor of acute kidney injury using starch-based volume replacement in the intensive care patients using propensity scoring methodology.

**References:**

Total number of peer reviewed publications in Pub Med: **20**

**Publications (List up to 5 recent publications relevant to proposed project)**


Person N. 6

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<tr>
<td>Daniel C Cattran</td>
<td>MD. Prof</td>
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Place of Birth (Country): Canada  
Present Nationality: Canadian  
Sex: Male  

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**- Major field of interest:**
- Glomerular diseases  
- IgA nephropathy  
- Proteinuric renal diseases  
- Risk factors for progression

**- Summarize the main outcomes of your research work/ programme(s) in the last 5 years (500 words maximum):**

My focus through my career has been in clinical research in glomerulonephritis. I created within the University of Toronto framework a network of connected nephrologists and nephropathologist interested in these disorders over 25 years ago. This platform has been maintained and continues to collect information on the natural history, and the effects of treatment of patients with glomerulonephritis in order to help identify factors related to progression and to develop treatment strategies to slow or prevent end-stage renal disease. Although initially limited to the Toronto area it has expanded to both national and international centers. I recognized, early on, the critical need for better predictors of those who would progress. My predictive algorithm developed for use in patients with membranous nephropathy clearly demonstrated improved sensitivity and specificity as well as better negative and positive predictive values compared to current practice at that time (Cattran, et al. KI, 1993).

I was the first to show a specific long-term renal protective benefit of angiotensin converting enzyme inhibition in preventing progression in patients with glomerulonephritis, specifically IgA nephropathy. This therapy is now considered a standard of care in this disease. I also developed a predictive algorithms for outcome in patients with IgAN (Cattran et al. AJKD 2001) recently validated in collaboration with a group from Scotland (Geddes et al NDT 2008). It was with this paper that I realized how limited are our current methods of predicting outcome. Using all known clinical, laboratory and histologic predictors, I was only able to explain 1/3 of the variation in disease progression rate. This led to the partnership that developed and subsequently published, the Oxford classification of IGA nephropathy (K. I. 2009).

Later, I recognized that RCTs in glomerulonephritis, required a broader base in order to acquire the proper sample size and still be feasible. I established the North American Nephrotic Syndrome Study Group involving multiple centres in both Canada and the United States. I was the organizer and senior author of multi-centre RCT’s one in membranous nephropathy and the other in focal and segmental glomerulosclerosis focusing on the use of Cyclosporine, a calcineurin inhibitor in patients with persistent nephrotic range proteinuria. Both studies showed a positive benefit that often persisted for years beyond the treatment period. Evaluation of new therapeutic agents in glomerular diseases remains one of my major objectives. Most recently culminating in senior authorship in a pilot trial of Rituximab in patients with membranous nephropathy. (KI, 2007). A recent thrust, (CIHR net grant), has laid the groundwork for the integration of translational physiology, basic biology and the psychosocial elements of disease related to progression of glomerulonephritis. This grant has opened up new avenues of investigation in the evaluation and treatment of patients with these glomerular disorders. This includes looking for new predictors of...
outcome in IgA nephropathy and other types of glomerulonephritis using genomic and proteomic techniques, part of this current proposed grant to the CIHR

<table>
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<tr>
<th>References</th>
<th>Total number of peer reviewed publications in Pub Med: 187</th>
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<tr>
<td><strong>Publications</strong> <em>(List up to 5 recent publications relevant to proposed project)</em></td>
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Table 1: Definitions of pathological variables used in classification of IgA nephropathy

* Mesangial score should be assessed in PAS stained sections. If more than half the glomeruli have more than 3 cells in a mesangial area this is categorised as M1. Therefore a formal mesangial cell count is not always necessary to derive the mesangial score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Score</th>
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<tr>
<td>Mesangial hypercellularity</td>
<td>&lt;4 mesangial cells/mesangial area = 0&lt;br&gt;4-5 mesangial cells/mesangial area = 1&lt;br&gt;6-7 mesangial cells/mesangial area = 2&lt;br&gt; &gt;8 mesangial cells/mesangial area = 3&lt;br&gt;The mesangial hypercellularity score is the mean score for all glomeruli</td>
<td>M0 ≤0.5  M1 &gt;0.5 *</td>
</tr>
<tr>
<td>Segmental glomerulosclerosis</td>
<td>Any amount of the tuft involved with sclerosis, but not involving the whole tuft or the presence of an adhesion.</td>
<td>S0 - absent  S1 - present</td>
</tr>
<tr>
<td>Endocapillary hypercellularity</td>
<td>Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina.</td>
<td>E0 - absent  E1 - present</td>
</tr>
<tr>
<td>Tubular atrophy/interstitial fibrosis</td>
<td>Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater</td>
<td>0-25% - T0  26-50% - T1  &gt;50% - T2</td>
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</tbody>
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## Oxford Classification of IgA nephropathy: Validation Study Scoresheet

### Centre
### Case Number
### Scorer
### Date

### Column A

<table>
<thead>
<tr>
<th>Mesangial cell hypercellularity</th>
<th>Total number of scorable glomeruli A</th>
<th>B</th>
<th>Mean mesangial score (B divided by A)</th>
</tr>
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<tbody>
<tr>
<td>no hypercellularity (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild (1) (4-5 cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate (2) (6-7 cells)</td>
<td></td>
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<tr>
<td>severe (3) (≥8 cells)</td>
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### Indeterminate

**Indeterminate mesangial cellularity due to:**

- Global sclerosis/advanced seg sclerosis
- Global endocapillary hypercellularity
- % Retracted tuft (ischaemic/collapse)
- % Less than 3 mesangial areas
- % Crescent only

### Total number of glomeruli

<table>
<thead>
<tr>
<th>Endocapillary hypercellularity</th>
<th>Segmental sclerosis/adhesion</th>
<th>GBM duplication</th>
<th>Necrosis</th>
<th>Cellular/fibrocellular crescent</th>
<th>Interstitial fibrosis/tubular atrophy to nearest 10%</th>
<th>Arteriosclerosis (score worst vessel) 0=absent,1=&lt;media,2=&gt;media</th>
<th>Arteriolar hyalinosis 0=absent,1=present</th>
</tr>
</thead>
<tbody>
<tr>
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### Column B

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<th>Total number of glomeruli</th>
<th>Global sclerosis/advanced seg sclerosis</th>
<th>Global endocapillary hypercellularity</th>
<th>% Retracted tuft (ischaemic/collapse)</th>
<th>% Less than 3 mesangial areas</th>
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<th>% Oxford Classification score</th>
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### Column C

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Appendix 1: Pathological definitions.

**IgA nephropathy:**
IgA nephropathy in the native kidney is defined as dominant or co-dominant staining with IgA in glomeruli by immunofluorescence or immunoperoxidase. Not all glomeruli need show this positivity. SLE-related nephritis should be excluded. The intensity of IgA staining should be more than trace. The distribution of IgA staining should include presence in the mesangium, with or without capillary loop staining, excluding a pure membranous, diffuse, global granular GBM staining pattern or linear GBM staining pattern. IgG and IgM may be present, but not in greater intensity than IgA, except that IgM may be prominent in sclerotic areas. Complement C3 may be present. The presence of C1q staining in more than trace intensity should bring up consideration of lupus nephritis.

**Glomerular definitions:**
- **Diffuse:** a lesion involving most (≥ 50%) glomeruli.
- **Focal:** a lesion involving <50% of glomeruli.
- **Global:** a lesion involving more than half of the glomerular tuft (NB see below for definitions of segmental and global sclerosis).
- **Segmental:** a lesion involving less than half of the glomerular tuft (i.e. at least half of the glomerular tuft is spared). NB see below for definitions of segmental and global sclerosis

**Endocapillary hypercellularity:** hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina.

**Increased mesangial matrix:** an increase in the extracellular material in the mesangium such that the width of the interspace exceeds two mesangial cell nuclei in at least two glomerular lobules.

**Sclerosis:** obliteration of the capillary lumen by increased extracellular matrix, with or without hyalinosis or foam cells.

**An adhesion:** an area of continuity between the glomerular tuft and Bowman's capsule separate from an extracapillary lesion or area of segmental sclerosis.

**Segmental sclerosis:** any amount of the tuft involved with sclerosis, but not involving the whole tuft.

**Global sclerosis:** the entire glomerular tuft involved with sclerosis.

**Collapsed/ischaemic glomerulus:** A glomerulus showing collapse of the capillary tuft with or without thickening of Bowman’s capsule and fibrosis in Bowman’s space.

**Extracapillary lesions** are subclassified as follows:
- **Extracapillary proliferation or cellular crescent:** extracapillary cell proliferation of more than two cell layers with ≥50% of the lesion occupied by cells. It is further classified by the percentage of glomerular circumference involved <10%, 10-25%, 26-50%, >50%.
- **Extracapillary fibrocellular proliferation or fibrocellular crescent:** an extracapillary lesion comprising cells and extracellular matrix, with <50% cells and <90% matrix. This is further classified by the percentage of the glomerular circumference involved <10%, 10-25%, 26-50%, >50%.
- **Extracapillary fibrosis or fibrous crescent:** >10% of the circumference of Bowman's capsule covered by a lesion composed of ≥90% matrix. It is further classified by the percentage of the glomerular circumference involved 10-25%, 26-50%, >50%. Ischaemic, obsolescent glomeruli should be excluded.

**A crescent** is one of these extracapillary lesions which involves >10% of the circumference of Bowman’s capsule.
**Mesangial hypercellularity** is subclassified as follows:
If <4 mesangial cells/mesangial area = normal,
4–5 mesangial cells/mesangial area = mild mesangial hypercellularity,
6–7 mesangial cells/mesangial area = moderate mesangial hypercellularity,
8 or more mesangial cells/mesangial area = severe mesangial hypercellularity.
Note: This is scored for each glomerulus by assessing the most cellular mesangial area. Mesangial
areas immediately adjacent to the vascular stalk should not be scored. Individual mesangial areas
showing hypercellularity are separated by areas of narrowing to the width of less than 2 mesangial
cell nuclei (ie count clusters, not files of mesangial cell nuclei).

**Tubulointerstitial definitions:**

**Tubular atrophy:** is defined by thick irregular tubular basement membranes with decreased diameter
of tubules. It is scored according to the percent of cortical area involvement with 1-5% rounded to
5% and other values rounded to the closest 10%.

**Interstitial fibrosis:** is defined as increased extracellular matrix separating tubules in the cortical
area. It is scored as percentage involvement with 1-5% rounded to 5% and other values rounded to
the closest 10%

**Interstitial inflammation:** is defined as inflammatory cells within the cortical interstitium in excess.
It is scored as percentage involvement with 1-5% rounded to 5% and other values rounded to the
closest 10%. It should be noted whether the inflammation is confined to areas of interstitial fibrosis
or not.

**Additional tubular lesions** are noted as follows: The presence of numerous red blood cells, defined
as tubules completely filled with red blood cells with or without casts, is noted as a lesion when it
involves >20% of tubules.

**Acute tubular injury** of the proximal tubular epithelium is defined by simplification of the
epithelium without tubular basement membrane thickening.

**Vascular definitions:**

**Arterial lesions** are scored based on the most severe lesions. Interlobular and larger arteries are
scored separately. An interlobular artery is one surrounded by cortex; an arcuate artery is one at the
corticomedullary junction. Intimal thickening is scored by comparing the thickness of the intima to
that of the media in the same segment of vessel. Score the intima variously as normal, and
thickened to more or less than the thickness of the media.

**Arteriolar hyaline** is noted as the proportion of arterioles affected (0, 1-25%, 26-50%, >50%).