

NEW RESEARCH TRENDS IN GASTROENTEROLOGY: PANCREATITIS IS IN DANGER

Ph.D. Thesis

Andrea Szentesi



First Department of Medicine, University of Szeged, Hungary
Institute for Translational Medicine, University of Pécs, Hungary
2017

**NEW RESEARCH TRENDS IN GASTROENTEROLOGY:
PANCREATITIS IS IN DANGER**

Ph.D. Thesis

Andrea Szentesi

Supervisors:

Prof. Péter Hegyi, M.D., Ph.D., D.Sc.

First Department of Medicine, University of Szeged
MTA-SZTE Momentum Translational Gastroenterology Research Group
Institute for Translational Medicine, University of Pécs

Áron Vincze, M.D., Ph.D.

First Department of Medicine, University of Pécs

Szeged

2017

Publications related to the subject of the thesis:

I) Andrea Szentesi, Emese Tóth, Emese Bálint, Júlia Fanczal, Tamara Madácsy, Dorottya Laczkó, Imre Ignáth, Anita Balázs, Petra Pallagi, József Maléth, Zoltán Rakonczay Jr, Balázs Kui, Dóra Illés, Katalin Márta, Ágnes Blaskó, Alexandra Demcsák, Andrea Párniczky, Gabriella Pár, Szilárd Gódi, Dóra Mosztbacher, Ákos Szücs, Adrienn Halász, Ferenc Izbéki, Nelli Farkas, Péter Hegyi

ANALYSIS OF RESEARCH ACTIVITY IN GASTROENTEROLOGY: PANCREATITIS IS IN REAL DANGER

PLOS One 2016 Oct 24;11(10):e0165244. **IF: 3.057**

doi: 10.1371/journal.pone.0165244.

II.) Andrea Párniczky, Balázs Kui, **Andrea Szentesi**, Anita Balázs, Ákos Szücs, Dóra Mosztbacher, József Czimmer, Patrícia Sarlós, Judit Bajor, Szilárd Gódi, Áron Vincze, Anita Illés, Imre Szabó, Gabriella Pár, Tamás Takács, László Czakó, Zoltán Szepes, Zoltán Rakonczay, Ferenc Izbéki, Judit Gervain, Adrienn Halász, János Novák, Stefan Crai, István Hritz, Csaba Góg, János Sümegi, Petra Golovics, Márta Varga, Barnabás Bod, József Hamvas, Mónika Varga-Müller, Zsuzsanna Papp, Miklós Sahin-Tóth and Péter Hegyi

PROSPECTIVE, MULTICENTRE, NATIONWIDE CLINICAL DATA FROM 600 CASES OF ACUTE PANCREATITIS

PLOS One 2016 Oct 31;11(10):e0165309. **IF: 3.057**

doi: 10.1371/journal.pone.0165309.

III.) Gábor Lakatos, Anita Balázs, Balázs Kui, Szilárd Gódi, Ákos Szücs, **Andrea Szentesi**, Zsolt Szentkereszty, Richárd Szmola, Dezső Kelemen, Róbert Papp, Áron Vincze, József Czimmer, Gabriella Pár, Judit Bajor, Imre Szabó, Ferenc Izbéki, Adrienn Halász, László Leindler, Gyula Farkas Jr, Tamás Takács, László Czakó, Zoltán Szepes, Péter Hegyi, Zsuzsanna Kahán

PANCREATIC CANCER: MULTICENTER PROSPECTIVE DATA COLLECTION AND ANALYSIS BY THE HUNGARIAN PANCREATIC STUDY GROUP

Journal of Gastrointestinal and Liver Diseases 2016 Jun;25(2):219-25. **IF: 1.891**

doi: 10.15403/jgld.2014.1121.252.pcr.

IV.) Andrea Párniczky, Eszter Hegyi, Anna Zsófia Tóth, Ákos Szücs, **Andrea Szentesi**, Áron Vincze, Ferenc Izbéki, Balázs Csaba Németh, Péter Hegyi, Miklós Sahin-Tóth

GENETIC ANALYSIS OF HUMAN ELASTASES CELA3A AND CELA3B TO ASSESS THE ROLE OF COMPLEX FORMATION BETWEEN PROELASTASES AND PROCARBOXYPEPTIDASES IN CHRONIC PANCREATITIS

International Journal of Molecular Sciences 2016 Dec 20;17(12). **IF 3,257**

doi: 10.3390/ijms17122148.

V.) Ákos Szücs, Tamás Marjai, **Andrea Szentesi**, Tamás Takács, László Czakó, Zoltán Szepes, Balázs Csaba Németh, Áron Vincze, Szilárd Gódi, Gabriella Pár, Imre Szabó, Patrícia Sarlós, Anita Illés, Ferenc Izbéki, Judit Gervain, Adrienn Halász, Andrea Párniczky, Gyula Farkas, László Leindler, Dezső Kelemen, Róbert Papp, Richárd Szmola, Márta Varga, József Hamvas, János Novák, Barnabás Bod, Péter Hegyi

CHRONIC PANCREATITIS. MULTICENTRE PROSPECTIVE DATA COLLECTION AND ANALYSIS BY THE HUNGARIAN PANCREATIC STUDY GROUP

PLOS One (accepted for publication: PONE-D-16-30039R1) **IF: 3.057**

Number of full publications: 5 (1 first author)

Cumulative impact factor: 14.319

LIST OF ABBREVIATIONS

AP: acute pancreatitis

CP: chronic pancreatitis

C-P: clinical pancreatitis

C-PC: clinical pancreatic cancer

E-P: experimental pancreatitis

E-PC: experimental pancreatic cancer

GI: gastrointestinal

IBD: inflammatory bowel disease

IBS: irritable bowel disease

IF: impact factor

PC: pancreatic cancer

K+F: kutatás és fejlesztés

UNDERSTANDING THE RESEARCH TRENDS IN GASTROENTEROLOGY

Introduction

By definition research and development (R&D) is a process of creating new products, processes and technologies that can be used and marketed for mankind's benefit in the future. The largest investor into and key player in health related R&D is the USA. The second largest investor into R&D is China and there is a strong will there to become a key leader in health related R&D and innovation in the future. In Europe, Germany, France, UK, Switzerland and Spain are the largest health related R&D spenders. Northern European countries are emerging from smaller countries thanks to their more intense investments in research and education. Remarkably, Central and Eastern European countries have little sources for health-related R&D.

In the last decade there was a serious global decrease in the business investment due to several reasons including the global financial crisis from 2008 through 2010 affecting seriously both central and industrial funding of research.

Aims

I. To understand the research trends in the field of gastroenterology and highlight the most endangered areas based on the gastrointestinal research publications in the last 50 years.

II. To identify possibilities of developing a better environment for pancreatic research and improvement of patient care within the framework of the Hungarian Pancreatic Study Group.

- Building patient registries and biobanks in pancreatic diseases
- Adapting Evidence Based Medicine (EBM) guidelines
- Education of doctors and students by publishing and presenting EBM guidelines

Methods

1. Analyzing scientific activity in the different areas of gastroenterology. In the first part of the study, we searched PubMed hits between 1965 and 2015 for pancreatic diseases (diabetes, pancreatitis and pancreatic cancer); benign gastrointestinal (GI) diseases (reflux, oesophagitis, Barrett's syndrome and gastritis, inflammatory bowel diseases, irritable bowel disease and hepatitis) and malignant GI diseases (gastric, oesophageal, colon, liver and pancreatic cancers). Altogether, 1,554,325 articles were analyzed.

2. Detailed analyses of basic and clinical studies on pancreatitis and pancreatic cancer. Since the biggest drop in research activity was in pancreatology, in the second part of the study we aimed to search PubMed for 'experimental pancreatitis' (E-P), 'experimental pancreatic cancer' (E-PC), 'pancreatitis AND clinical trial' (C-P), 'pancreatic cancer AND clinical trial' (C-PC). Altogether, 14,255 articles were analyzed. All the available abstracts were checked. The final analyses were only performed on articles which contained original data in pancreatic research (6,628) in the categories described above. After the exclusions, we conducted a detailed analysis of 1,871 articles in E-P, 1,726 in E-PC, 1,079 in C-P and 1,952 in C-PC. The following parameters were collected from the articles: (1) number of countries, (2) countries, (3) number of centres, (4) the journal's impact factor and (5) whether the trial was registered in an official trial registry (only for clinical trials). An article was defined as 'multinational' if more than five countries were involved and 'multicentre' if more than five centres took part in the research. Analyses were performed for individual countries. An analysis of the individual parameters was conducted on the group of articles where the given parameter was available.

3. Statistical analysis

To investigate differences in research activity, we compared the confidence intervals (CI) of the proportions. To analyze the changes of research activity, we compared the slopes of the regression with an estimation of CI. One-way ANOVA was used with Dunnett's post hoc test (unequal variances were assumed) to compare the IF between countries and centres. Chi-square tests were employed for relationship analysis. Statistical analyses were done by IBM SPSS Statistics v 20.0 (IBM Corporation, Armonk, NY, USA). Values are expressed as means \pm standard error (S.E.M.) if not stated otherwise. A *P* value <0.05 was considered statistically significant.

Results

1. Research activity on pancreatitis has decreased compared to other gastrointestinal diseases. In the first part of the study, we characterized research activity on different parts of the GI tract. In 1965, among the major benign GI disorders, 51.9% (CI 49.58–54.22) of the research was performed on hepatitis, 25.7% (CI 23.63–27.75) on pancreatitis, 21.7% (CI 19.76–23.30) on upper GI diseases and only 0.7% (CI 0.34–1.13) on the lower GI disorders. Half a century later, in 2015, twelve times more research was being carried out on benign GI disorders. Research on the lower GI tract had increased 383 times, that on hepatitis eleven times and that on the upper GI tract ten times, the number of studies on pancreatitis had risen only five times. Only 10.7% (CI 10.27–11.11) of the research activity in 2015 was being performed on pancreatitis. We can assume that the great loss of interest in pancreatology was accompanied by a great upturn in research in the lower GI disorders, namely, inflammatory bowel diseases (IBD) and irritable bowel disease (IBS).

2. Research activity on pancreatic cancer has risen slightly compared to other GI cancers. In 1965, among the major malignant GI disorders, research was conducted on the different forms of cancer as follows: cancer of the liver: 33.9% (CI 31.89–35.93); the stomach: 29.1% (CI 27.18–31.04); the colon: 14.6% (CI 13.05–16.05); the pancreas: 11.9% (CI 10.55–13.29); and the oesophagus: 10.5% (CI 9.20–11.80). Fifty years later, in 2015, twelve times more research was being performed on malignant GI disorders, an increase of exactly the same level as that of the studies on the benign GI disorders. While the relative research activity on liver and oesophageal cancer did not change, a clear decrease was observed in studies on gastric cancer (from 29.1% to 20.2%), with the biggest rise found in the research on pancreatic cancer.

3. Research on pancreatitis has decreased compared to that on other major pancreatic disorders. Since the biggest drop in GI research interest was in the area of pancreatitis, we continued our study by analyzing the trends in pancreatic diseases. Here we compared the changes of research activity in diabetes, pancreatitis and pancreatic cancer. In 1965, 71.8% (CI 69.99–73.51) of the research was performed on diabetes, 18.1% (CI 16.63–19.65) on pancreatitis and 10.1% (CI 8.93–11.29) on pancreatic cancer. Although 18 times more studies were being conducted on the pancreas 50 years later, the relative interest in pancreatitis had dropped to 5% (CI 4.88–5.28). The relative activity did not change very much in pancreatic cancer (from 10.1 to 11.2%); however, research interest in the endocrine pancreas rose by

11.9%. Analyzing the dynamic of the changes, we can assume that the biggest rise in pancreatic research activity in the last five years was in experimental pancreatic cancer.

4. The USA, Germany and Japan published the highest number of articles in pancreatology. As stated above, 6,628 articles contained original research on basic or clinical pancreatology. Regarding the continents, 47.8% of all participation involved Europe, 28.8% North America, 20.4% Asia and the Middle East, 1.2% Australia and Oceania, 1.2% South America and 0.5% Africa. Regarding the location of research, not surprisingly, countries with the largest population had an advantage: the USA was involved in the largest number of research articles (26.8%), followed by Germany (10.4%), Japan (10.2%) and China (6.4%). Altogether, these four countries participated in more than 50% of the research on pancreatology. Detailed analyses of the four subgroups revealed that the USA led all four subgroups. The countries that ranked second in the subgroups were Germany in the experimental research groups (E-P and E-PC), China in C-P and Japan in C-PC.

5. The density of active pancreatic researchers is highest in the Scandinavian countries.

Comparing the data per population of 10 million, small countries came to the fore. Scandinavian countries are clearly the most active in pancreatic research per capita. None of the big countries were in the top five. Detailed analysis has also revealed that E-P research is led by Finland, E-PC by Switzerland, C-P by Denmark and C-PC by Sweden.

6. The USA and the Netherlands are in the forefront in registered clinical trials. The highest level of evidence is obtained from registered clinical trials. Unfortunately, only 13.4% of all trials were registered in our analysis of the period between 1965 and 2015. With regard to the absolute numbers of registered clinical trials in pancreatology, the big countries register the highest number of trials. Comparing registered clinical trials per person, Dutch researchers have been the most active, followed by Hungary, Denmark and Sweden.

7. Multinational and multicentre studies provide the most valuable research in pancreatology. Detailed analyses showed that there are no big differences between the average impact factors (IF) of countries. Therefore, the quality of research is not country-dependent. However, detailed analysis of the articles revealed that there is a strong correlation between the

number of countries per study and the quality of the article. In a single-nation article, the average IF is $4.652 (\pm 0.10)$, when only a single centre is involved. The involvement of more than six centres in a single nation increased the average IF of articles to $7.094 (\pm 0.37)$. Notably, multicentre and multinational studies achieved the highest average impact $19.278 (\pm 2.55)$.

Discussion

What did we find and what can we do?

Strengths: Both large and small countries are contributing to pancreatic research. The literature on pancreatology is dominated by the United States, Germany, China, Japan, Italy and the UK, just like in other scientific fields, such as ‘pain’ and ‘oncology’. The same countries have the highest R&D funds, whereas the density of pancreatic research is the highest in the Netherlands, Finland, Sweden, Denmark and Hungary. We have observed a positive trend in the publication of pancreatic cancer research, although the reason is definitely the highest corporate funding share in oncology and multifactorial action plans, such as those in the USA and Europe, which increase awareness and may influence decision makers and promote grant funding.

Weaknesses: There are 50 countries in Europe, but only 23 are actively publishing in the field. The majority (84.8%) of the articles under analysis represent a single nation, and 39.9% are single-nation and single-centre studies. Not surprisingly, without cooperation, the possibilities for data collection were limited; therefore, only a few high-quality multinational and multicentre observational clinical trials or randomized controlled trials (RCT) were performed. It is important to highlight that the Central and Eastern European, African, South American and Asian countries are facing the biggest difficulties as their sometimes poor infrastructure and lack of resources make them an undesirable research partner. Moreover, grant proposals submitted from these countries are usually rejected. More than 50% of the European countries (representing more than 200 million people!) are only slightly involved in pancreatic research.

Opportunities: This analysis provides clear evidence that multicentre, multinational cooperation can achieve better-quality trials and higher impact in the field. International patient registries and biobanks should be created to stimulate quality multicentre observational trials, RCTs and translational research. Importantly, following the success of pancreatic cancer action plans that probably contributed to the four-fold rise of E-PC research activity in the last few years, the same action should be initiated for pancreatitis.

Threats: If research on pancreatitis is to decrease further, journal editors may consider pancreatology an even lower priority, thus resulting in fewer publications in top journals, which

will probably be followed by fewer grants and less activity in the field, thus continuing the vicious circle seen in the last 50 years, which has resulted in no specific treatment for acute pancreatitis.

Conclusion

Countries that have the largest biomedical R&D investments, like the USA, Japan, and Germany, publish the highest number of scientific papers. Smaller countries with much less sources, like Sweden, Finland, Denmark or Hungary, may increase their impact by more intense financial and human resource R&D investments and also by international co-operations.

Substantially more academic and other clinical research should be performed in gastroenterology providing higher evidence for more therapeutic solutions. Activity in pancreatitis research has been rapidly decreasing. These data strongly suggest to governments, industry and non-profit organizations that they should consider pancreatitis an endangered field of research and sponsor far more international networks and academic R&D activities.

DEVELOPING A BETTER ENVIRONMENT FOR PANCREATIC RESEARCH

Introduction

As our previous analysis showed, industrial investments into gastroenterology research has been decreasing in the last decade just like the activity in pancreatology research, especially concerning pancreatitis. This analysis has also confirmed that multinational-multicentre trials are of higher quality, providing higher evidence and impact, but the share of the multinational-multicentre studies are very low. Consequently, there is still much space for improving both the quantity and quality of research activity in the field of pancreatology. In this chapter I would like to sum up of steps the Hungarian Pancreatic Study Group has made as a start for improvement.

Aims

Our aims were to collect clinical data and biological samples prospectively for further studies in acute pancreatitis (AP), chronic pancreatitis (CP) and pancreatic cancer (PC), to recruit centres in order to increase the quality of the research, to provide a database and biobank for pancreatic research open for all participants and to make the results widely available, open access. Building on the experiences, findings and joined centres of the patient registries, the further aim of the Hungarian Pancreatic Study Group was to plan and conduct observational and randomized controlled clinical trials and improve the management of pancreatic patients by adapting the international evidence-based guidelines and educating doctors and students.

Methods

Research plan: the research plan should include the research protocol, the research questionnaire, the patient information form, the patient informed consent form and the participation agreement of the joining centers.

Ethical approval: For developing a registry and a biobank, a research plan should be approved by the Secretary of Medical Research Council, Scientific and Research Ethics Committee.

Recruiting centres: the registry and biobank is open for every institution that is able to collect all necessary data.

Patient enrollment: the patient should be informed on the purpose of the research and blood sampling and the Patient Informed Consent Form should be signed before any enrollment.

Data collection: As data registration should be available at the different institutions, the HPSG has developed a web-page and a web-based electronic data administration system. All forms are available from the website and data upload can be accomplished online.

Collected clinical data: the collected information is different for every diagnosis and may include details from the patient's medical history, risk factors, etiology, symptoms and clinical signs, details of physical examination, laboratory parameters, imaging examinations, other examinations, conservative, endoscopic, surgical, oncological and supportive therapy details and complications.

Collected samples: the collection, delivery and storing of blood samples and other biological samples are processed according to the protocol.

Data quality control: there is a four-step controlling of data in the registry (local and central administrative and professional controlling).

Data and sample access: actively contributing and collaborating researchers may access to data and samples after a formal application with a full scientific proposal. The use of samples and data are free of charge and should serve research purposes only.

Publications: any results based on the data of the HPSG Registry for Pancreatic Patients, can only be published with the consent of the HPSG.

Results

1. Establishing the Registry for Pancreatic Patients.

The Hungarian Pancreatic Study Group (HPSG) was founded in 2011 and started the process of developing a national, then an international multicenter network for pancreatic research.

The National Pancreas Registry was started in 2012, after receiving the necessary ethical permissions, collecting clinical data of acute and chronic pancreatitis and pancreatic cancer cases and biological samples. To involve more and more Hungarian centers it was necessary to individually contact them and organize trainings on patient enrollment and data administration. A functional webpage and a data administration system was developed, that made possible for the centers to directly upload data into the electronic database. The registry started with one Hungarian center in Szeged, soon, the number of joined Hungarian centers and enrolled patients started to grow rapidly, reaching 26 centers and 1200 patients in 2014. After 2014 international centres are contributing also to the development of the registry. In 2016, 39 institutions from 4

countries are uploading data to the AP, CP and PC general registry, 33 institutions from 23 countries to the trial database but altogether 99 centres have joined or in the process of joining.

2. Analyses based on registry data and biological samples.

Based on the HPSG Registry for Pancreatic Patients several genetic and three cohort studies have been completed and published.

Pancreatic cancer. Multicenter Prospective Data Collection and Analysis by the Hungarian Pancreatic Study Group.

354 patients with pancreatic cancer were enrolled into our registry from 14 centres between September 2012 and March 2014. This Hungarian cohort provided useful information on demographics, the frequency of recurrent AP and CP in the medical history, histological type, details on endoscopic management of obstructions and independent predictors for overall survival.

Prospective, Multicentre, Nationwide Clinical Data from 600 cases of Acute Pancreatitis.

600 patients were enrolled prospectively between January 2013 and January 2015 from 17 Hungarian centres. The nationwide cohort of 600 cases of AP has showed the major determinants and associations of severity and mortality in AP and also emphasized the importance of the compliance to evidence-based guidelines.

Chronic pancreatitis. Multicenter Prospective Data Collection and Analysis by the Hungarian Pancreatic Study Group. 229 patients were enrolled between 2012 and 2014 from 14 Hungarian centres. The first nationwide prospective data collection provided important information for improving the treatment of the disease. However, quality of data collection on diagnosis details and on the progression of the chronic disease should be improved.

Genetic Analysis of Human Chymotrypsin-Like Elastases 3A and 3B (CELA3A and CELA3B) to Assess the Role of Complex Formation between Proelastases and Procarboxypeptidases in Chronic Pancreatitis This genetic study was completed on samples from 225 unrelated patients with CP (including 120 with alcoholic CP and 105 with idiopathic CP) and 300 controls with no pancreatic disease. Individuals were enrolled to the HPSG Registry for Pancreatic Patients from 11 Hungarian centers between 2012 and 2016.

The study demonstrated that variants affecting amino-acid position 241 in human CELA3A and CELA3B are not associated with CP, indicating that changes in complex formation between

human proelastases and procarboxypeptidases do not influence the risk for CP. The observation that intronic variant c.643-7G>T in CELA3B was significantly underrepresented in alcoholic CP patients suggests this might be a protective variant.

3. Becoming multinational. In November 2014, the 3rd Conference of the Hungarian Pancreatic Study Group was organized together with the 9th International Symposium on Alcoholic Liver and Pancreatic Diseases and Cirrhosis, making the event an excellent occasion to involve international participants and the Eastern and Central European Pancreatic Study Group was founded. This way, the National Pancreatic Registry, has become international, just like the multicenter observational clinical trials initiated by the HPSG.

4. Planning and developing observational clinical studies. The HPSG initiated four multicenter, observational clinical trials, namely: 1) EASY for establishing an easily obtainable, accurate clinical scoring system that can stratify patients according to the severity of acute pancreatitis in the first 6-12 hours after admission, 2) PINEAPPLE to establish a clinical scoring system to evaluate the necessity of pancreas enzyme test or imaging examination when a child appears at the emergency unit with abdominal pain, 3) APPLE for exploring the course of pediatric pancreatitis and specify the genetic background of the disease and 4) PREPAST to evaluate the role of preventive pancreatic stents at the early course of acute biliary pancreatitis evaluating complications and overall outcome compared to the standard ERCP techniques. 33 international centers have already actively contributing to the trials, from 23 different countries and additional 30 centres have expressed their intent to join, several of them are under the process of acquiring the local ethical permission.

5. Adapting evidence based guidelines. In 2014 The Hungarian Pancreatic Study Group proposed to prepare Evidence Based Guidelines for the management of acute pancreatitis, chronic pancreatitis, autoimmune pancreatitis, pancreatic cancer and pediatric pancreatitis. The international guidelines were translated and completed or modified where it was necessary by the preparatory and consultant team appointed by the HPSG. The guidelines were presented, discussed and accepted on a consensus meeting held on 12th September 2014.

6. Educating young doctors and students. The HPSG is committed to improve the lives of patients suffering from pancreatic diseases. To disseminate the EBM guideline for pancreatic diseases, the HPSG printed a hard copy of the published Hungarian guidelines. The

book is available at the conferences and can be ordered directly from the study group. As the compliance to the guidelines are crucial for a better management of the diseases, the HPSG is organizing training courses and presentations at conferences and at universities.

Conclusions

Current barriers in pancreatology should be eliminated by an international research network, cooperation between pancreatic communities in different countries that will result in more and higher quality prospective multicenter observational clinical trials and RCTs, EBM guidelines available in more countries, improvement of compliance through education, influence on national financing of pancreatology, ultimately in quality research. To reach this goal, transparency, trust, visibility and teamwork are absolutely essential. The Hungarian Pancreatic Study Group undertakes the task of coordination and administrative support and it is open for initiatives and ideas.

New results

Analyzing the research trends in gastroenterology

1. From 1965 to 2015, the great loss of interest in pancreatology was accompanied by a major increase of research in the lower GI disorders, namely, IBD and IBS.
2. Among the malignant GI diseases the biggest increase was found in research activity on pancreatic cancer.
3. Concerning pancreatic diseases (pancreatitis, pancreatic cancer, diabetes), the relative interest in pancreatitis dropped from 18.1% to 5%.
4. The USA, Germany and Japan published the most scientific papers in pancreatology and this is parallel with the R&D investment shares except for China where the investment has increased substantially only in the last few years.
5. The Scandinavian countries are clearly the most active in pancreatic research per capita and this is most probably caused by the higher R&D intensity and human resource investments in these countries.
6. Multicentre and multinational clinical trials provide the highest impact in pancreatic research.

Developing a better environment for pancreatic research

1. Improving the Registry for Pancreatic Patients – data collection, documentation, electronic surface, centre enrollment, data analysis.
2. Participation in data analysis based on the Registry for Pancreatic Patients, resulting in published articles.

ACKNOWLEDGEMENTS

I would like to express a very special thanks and my most sincere gratitude to my mentor and supervisor, **Professor Péter Hegyi**, at the First Department of Medicine, University of Szeged and Institute for Translational Medicine, University of Pécs, who made me feel I am capable of valuable achievements, who provided continuous scientific and methodological guidance and also secured the substantial financial and personnel background for the research and achievements described in this work.

I would like to express my gratitude also to my other supervisor, **Dr. Áron Vincze** at the First Department of Medicine, University of Pécs, who supported me with his valuable advices and comments on my thesis.

I am grateful to **Professor György Ábrahám**, the head of the First Department of Medicine, University of Szeged who made me possible to work at his department.

This work would not have been possible to accomplish without the support and active participation of **all the members of the Hungarian Pancreatic Study Group** and the **Pancreas Laboratory** at the University of Szeged, especially (in alphabetical order) **Márta Bába, Dr. Anita Balázs, Emese Réka Bálint, Zsolt Balla, Erika Darvasi, Dr. Alexandra Demcsák, Júlia Fanczal, Nelli Farkas, Rea Fritz, Erzsébet Zoltánné Fuksz, Dr. Szilárd Gódi, Dr. Adrienn Halász, Krisztina Harth, Dr. Imre Ignáth, Dr. Dóra Illés, Dr. Ferenc Izbéki, Dr. Máté Katona, Ágnes Kocsisné Halas, Balázs Koncz, Dr. Balázs Kui, Dr. Dorottya Laczkó, Dr. Gábor Lakatos, Tamara Madácsy, Edit Pálfi Magyarné, Dr. József Maléth, Dr. Katalin Márta, Zsuzsa Miklósné Árva, Dr. Tímea Molnár, Dr. Dóra Mosztbacher, Dr. Balázs Németh, Dr. Petra Pallagi, Dr. Gabriella Pár, Dr. Andrea Párniczky, Dr. Dániel Pécsi, Tünde Pritz, Dr. Zoltán Rakonczay, Zsuzsanna Répásy, Dr. Anikó Nóra Szabó, Dr. Ákos Szücs, Emese Tóth, Dr. Péter Varjú, Dr. Viktória Venglovecz** and all the contributors to the Registry for Pancreatic Patients, a very special thanks to them.

Last but not least I am extremely grateful to my husband, **László Madarász**, who inspired me with his valuable advices and made me possible to work long hours on my research and thesis, sharing and often undertaking the responsibility and tasks with our family of three children beside his responsible job. I would also like to thank our children, **Réka, Ákos and Attila Madarász** for all their patience and help while I was occupied by this work, especially that Réka and Ákos are having their graduation and university entrance exams this year.

FINANCIAL SUPPORT

The study was supported by the Hungarian Academy of Sciences – University of Szeged, Momentum Gastroenterology Multidisciplinary Research Group (960152 to Péter Hegyi), the National Research, Development and Innovation Office (K116634 to Péter Hegyi) and the Economic Development and Innovation Operational Program (GINOP-2.3.2-15, University of Pécs).