Focus on Complement

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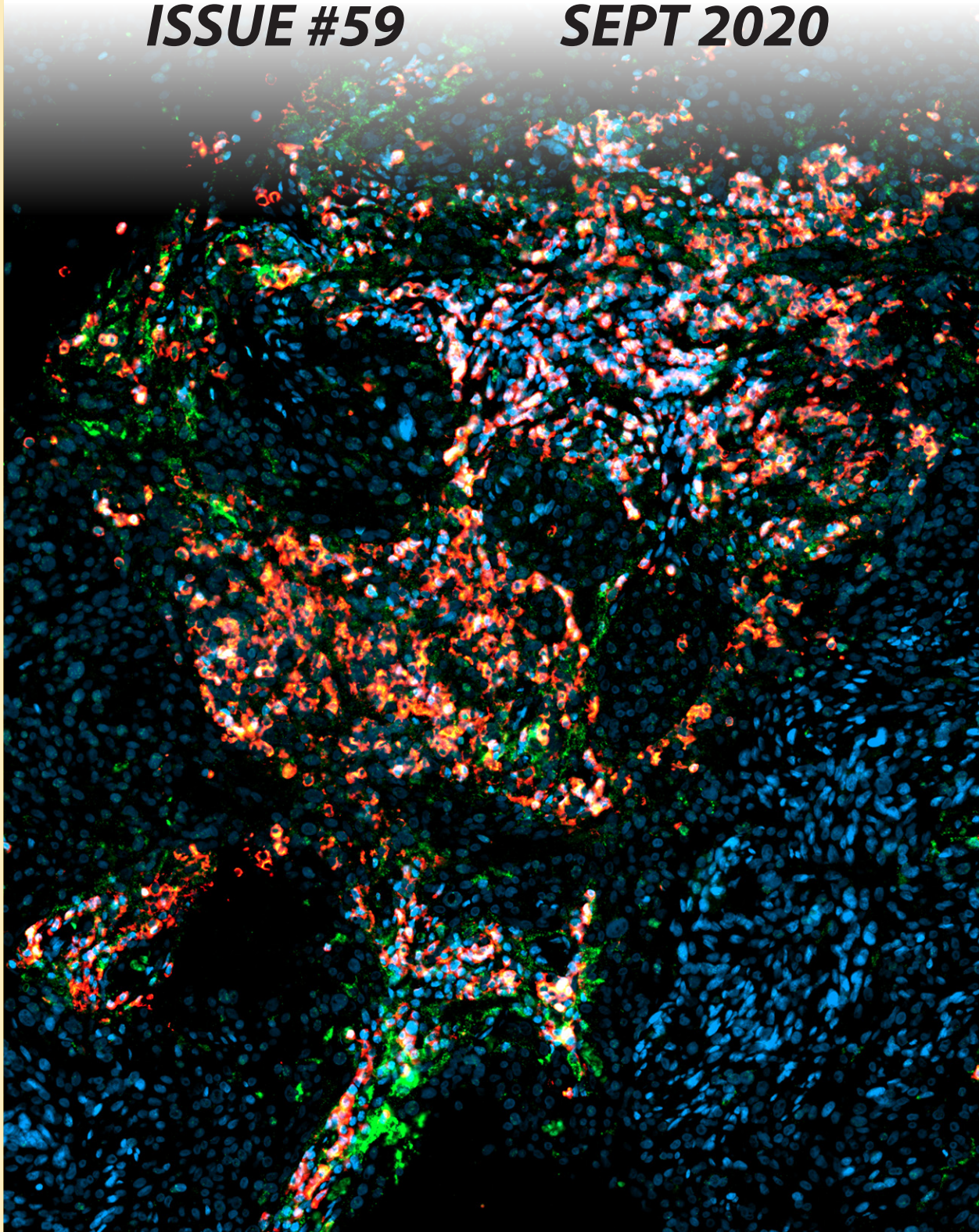

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Focus on Complement

Issue #59

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In this 59th Issue of Focus on Complement:

From the Editor

Dear Readers,

Welcome to the 59th Issue of *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

In this issue, Professors Claudia Kemper and Andrea Tenner present the winners of the *Pioneering Women in Complement Awards* for 2020, and we highlight their outstanding research contributions to our field. This also includes a particularly poignant memorium for winner, Professor Jarmila Janatova.

We also congratulate Dr Stefan Sonderegger who is the winner of the FoC Early Career Cover Image Award. A description of his research and cover image can be found in the following pages. We also feature the research groups of Professor Dr Bert van den Heuvel, Dr Elena Volokhina and Dr Nicole van de Kar from The Netherlands, and Professor Simon Clark from Germany. Issue contributor Professor Peter Zipfel reviews two articles that examine mechanisms of complement activation by SARS-CoV-2, and complement's contribution to sex bias for disease susceptibility.

Finally, the ICS has organised a special online symposium discussing complement in COVID-19 (Oct 28th, details on Page 21). We encourage you to attend.

I hope you all enjoy this September 2020 issue of *Focus on Complement*, and wish everyone safe times ahead.

Trent Woodruff, PhD.
Editor, FoC
Secretary, ICS

Connect with the ICS

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Trent Woodruff (t.woodruff@uq.edu.au) or Peter Garred (Peter.Garred@regionh.dk).

Plus visit our website and follow us on Twitter to keep updated with the latest ICS and complement news.

www.complement.org @complementsoc

Stefan Sonderegger: Winner of the Focus on Complement Early Career Cover Image Award

Mag. Dr. Stefan E. Sonderegger is a Research Fellow in the laboratory of Dr Barbara Rolfe at the Australian Institute for Bioengineering and Nanotechnology (AIBN). Stefan came to Australia in 2010, where he worked for eight years as a Postdoc at the Australian Centre for Blood Diseases at Monash. Together with Cancer Therapeutics CRC, Stefan investigated clinical applications of a new inhibitor against PRMT5 (an arginine methyltransferase). He worked with Merck (MSD Australia) to develop IP which was licensed in a multi-million dollar package. Since joining AIBN in 2019, Stefan's research has focussed on harnessing the innate immune system to target cancer.

Cover Image Description: Immunofluorescence staining shows human melanoma tissue infiltrated by immune cells (CD45+, yellow), mainly macrophages (CD68+, **red**), many of which express C3aR (**green**); nuclei are stained with DAPI (**blue**). Our research suggests that complement activation within the tumour microenvironment promotes the infiltration of immunosuppressive myeloid cells, including tumour-associated macrophages (TAMs), which promote tumour growth.

The ***Early Career Cover Image Award***. Each Issue the ICS board will select a scientific image to highlight on the front cover of FoC. The winning image will include a brief description of the image, and a profile of the winner within the newsletter.

Eligibility: graduate students, post-doctoral staff, and early career researchers (generally, but not exclusively under 40 years of age) are eligible to apply.

Interested applicants should email the FoC Editor (t.woodruff@uq.edu.au) at least 2 weeks prior to each issue release date (release dates: 1st March, 1st June, 1st September, 1st December), with one suggested image of their research. Images could include immunochemistry (tissues, cells etc), pathology, structures, or any other image of relevance to complement research. All images should not have any copyright that would be infringed if published in FoC (for example work already published in a journal). Submissions should also include a brief profile of the researcher and a description of the image (~100 words each).

Winners of the Award will additionally receive a signed certificate from the ICS.

Pioneering Women in Complement Research Award

As representatives of the complement community, it is our honor to award the first 'Pioneering Women in Complement Research Award' to Professors Patricia Creveling Giclas, Irma Gigli, and the late Jarmila Janatova.

This award was initiated to honor retired female members of the complement community for their major and long-lasting scientific impact on our research field – and to showcase key female complementologists as role models for the younger female scientists among us.

Our understanding of the biological pathways that underly human health and diseases is shaped by the countless scientists that constantly pushed and push the boundaries of our knowledge. For many decades, scientific research was dominated at the bench and in central academic leadership positions by male investigators. Women only broke slowly into these ranks and many of them had to work 'double-hard' to not only garner scientific success but to simultaneously raise children. Thus, 'early' independent female scientists, such as the awardees that we honor here, are true trailblazers and paved the way for the next generation of female scientists.

Whilst the names of famous women in history books that contributed vitally and cross-disciplinary to science is constantly increasing and the prospects of women in science have never been better than they are now, significant gender-based disparities remain, including disparities in recognition, salary, and funding (1). Furthermore, the COVID-19 pandemic has shown us, that female scientists, particularly those at earlier career stages, remain unproportionally more vulnerable to 'adverse events': they most often bear the greater proportion of childcare and household responsibilities, which impacts negatively on their ability to do or direct lab work and to publish. Indeed, the numbers of biomedical publications with female first authors dropped by 19% and that of female senior authors by 5% this year (2).

Thus, in honor and the spirit of the Pioneering Women in Complement Research, this is a prime time for the complement community to come together and not only celebrate our awardees but to also protect particularly our next generation of female scientists – and actions of each single lab head or institute director can support this cause.

In the following are contributions from John P. Atkinson and Ashley Frazer-Abel that highlight the careers and contributions of Prof. Irma Gigli and Patsy Giclas, respectively. Sadly, Prof. Jarmila Janatova passed away on July 13th of this year. David Isenman and Andrea Tenner have composed a memorial to honor her life.

Claudia Kemper and Andrea Tenner

1. Carr, P. L. et al. Gender differences in academic medicine: retention, rank, and leadership comparisons from the National Faculty Survey. Acad. Med. 93, 1694–1699 (2018).

2. Andersen, J.P. et al. COVID-19 Medical Papers Have Fewer Women First Authors Than Expected. eLife Vol. 9, Article No. e58807 (2020).

Pioneering Women in Complement Research Award

Irma Gigli, M.D.

Irma Gigli is Professor Emeritus at the University of Texas, Houston where she served as The Walter & Mary Mischer Distinguished Professor in Molecular Medicine, The Hans J. Müller-Eberhard Chair in Immunology, and the Director of the Brown Foundation Institute of Molecular Medicine Center for Immunology & Autoimmune Diseases.

Dr. Irma Gigli received her undergraduate education in Argentina. In the "States" she did her medical residency at Cook County Hospital in Chicago, Illinois followed by basic research training in complement at New York University. She next undertook three years of complement focused protein chemistry studies at the Howard Hughes Medical Institute in Miami, Florida. This was followed by two years in Germany (University of Frankfurt) before she joined the faculty at Harvard Medical School, where she worked until 1976. After a 'stint' in Oxford, UK, and a brief Professorship at New York University, she accepted a post as Chief of the Division of Dermatology at UC San Diego. In 1992, she moved to UT Houston where she was appointed Professor of Medicine and Dermatology, Vice-Chair of Medical Sciences and co-founded the Brown Foundation Institute of Molecular Medicine Center for the Prevention of Human Diseases at UT Houston for which she initially served as its Deputy Director.

Dr. Gigli has won numerous prizes throughout her remarkable scientific career including being an elected member of the Board of Scientific Counselors of the National Institute of Allergy and Infectious Diseases and of the Board of Directors of the US Civilian Research and Development Foundation. In 2003, Dr. Gigli received the Distinguished Professional Woman of the Year Award from the University of Texas Health Science Center at Houston. She is the recipient of the 2005 David Martin Carter Mentor Award from the American Skin Association, and also received the Stephen Rothman Memorial Award from the Society for Investigative Dermatology. Dr. Gigli is an Honorary Member and Past-President of the Society for Investigative Dermatology. She is also a member of the American Society for Clinical Investigation, the International Complement Society, the Association of American Physicians, the American Academy of Dermatology, the Institute of Medicine of the National Academy of Sciences, and a Fellow of the American Academy of Arts and Sciences. She serves on the Board of Directors for the Academy of Medicine, Science & Engineering of Texas. She has been on a number of national and international committees dealing with education and health in the US and third world countries. She is on the Board of Directors of the International Community Foundation in San Diego, and the Board of Directors of the US Civilian Research and Development Foundation.

Several of her outstanding contributions to the field of complement research include the following:
1) Application to a specific clinical field. As a clinical (Dermatology) academic, she was among the first physician-scientists working at the interface of basic immunology and skin diseases. Dr. Gigli was one of the early physician-scientists who was able to successfully bridge basic immunology with clinical dermatology. In fact, her efforts in this important area of translational research led to the formation of the first NIH sponsored program in "Immunodermatology".

Pioneering Women in Complement Research Award

2) Phylogeny. She is also particularly known for her studies on the evolution of the complement systems' regulatory proteins, FH and C4b binding protein, and of the early components of the classical pathway including C1q, C1r, C1s, C4 and C2. Her basic science work has always had as its fundamental underpinning the relevance of basic science research to human disease. This goal was a strong motivator for her to accept a leadership position in the creation and development of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases in 1995, along with her late husband, Professor Hans J. Müller-Eberhard, the Founding Director of the Institute.

3) Pathogens and Complement. She was the first to demonstrate that proteases from a pathogen (*Entamoeba histolytica*) can degrade complement effector proteins such as C3b and anaphylatoxins. This key observation led to many subsequent studies on multiple other pathogens who either hijacked our regulators or synthesized their own mimic.

4) Her exemplary career as a mentor. Above all, she is recognized as an outstanding and life-long mentor to the many clinical and basic research students and fellows she trained during her career. *Claudia Kemper would like to add a personal note:* "Professor Irma Gigli was my primary PhD supervisor whilst I was trying to unlock the capabilities of complement regulatory proteins in fish. Many in the field who know Irma, will not be surprised if I share with you that my initial time in her lab was not all smooth sailing. Irma was a very hands-on supervisor (she personally taught me several techniques including the CH50 test), but was also highly demanding and very critical and direct – little of the work I did initially passed her muster and I was often frustrated. It took me time to actually appreciate the effort and hours Irma put into my training, specifically since she had many other duties as Co-Director of an Institute – but we then developed a strong and well-functioning supervisor-trainee relationship. By the end of my PhD, I had fallen in love with the complement system and was determined to pursue a career in immunology. Irma not only laid the foundation for me to do so but has remained a mentor and friend throughout my career. I have (and still do) asked her for advice often, for example, before making important career decisions and I try to pass on to my team and trainees what I have learned from her. Thus, Irma's influence truly resonates through my scientific life, and I am very pleased to see her receiving the 'Pioneering Women in Complement Research Award' ".

Her extensive training and collaborations with multiple pioneers in the complement field were envied by many of us. Beginning in Florida with Robert Nelson (which included a 1962 paper where they purified all nine components of the classical pathway in the guinea pig), multiple seminal publications with K. Frank Austen and colleagues at Harvard on the phylogeny of the subcomponents of C1, C4 and C2 in multiple species, informative studies with Victor Nussenzweig at New York University including key reports on CR1 and the plasma regulators and fundamental studies on the early components of the classical pathway with Rodney Porter and colleagues in London. Irma's close connections with some of the giants in the complement field also extended into her private life: Irma was married to Hans J. Müller-Eberhard the premier complement protein chemist of his time – a rather amazing story – with whom she then co-founded the Institute at the University of Texas, Houston. As noted by Claudia Kemper "On top of this, Irma was known for her love of fashion and there was arguably no other female PI in the field during her time that looked as 'chique' in a lab coat as Irma".

Pioneering Women in Complement Research Award

To further summarize her scientific accomplishments, she has published over 160 original manuscripts and book chapters, many of which identified basic mechanisms involved in host defense and in the development of skin diseases. Her expertise is not limited only to the crossroads of clinical immunology and dermatology but also many contributions to our understanding of the basic biology of the complement system. In her career, she has always been fully committed to the vision that the quality of life of mankind can be greatly improved by understanding the mechanisms of the diseases that afflict them and that advances in biomedical sciences can prevent disease occurrence.

*Multiple individuals attributed to this tribute including Claudia Kemper (who trained with Irma), Laura Simon, (Research Support Librarian at the Bernard Becker Medical Library at Washington University School of Medicine who pulled together the publication record and citation data) and Madonna Bogacki for manuscript preparation.

John P. Atkinson, M.D.

Irma Gigli, M.D.

Winner: Pioneering Women in Complement

Pioneering Women in Complement Research Award

Patricia C. Giclas, Ph.D.

It was my honor to nominate Patricia C. Giclas for the Pioneering Women in Complement award and I was delighted to hear she was chosen as an awardee with such distinguished company as Dr. Gigli and Dr. Janatova. When Dr. Giclas learned of her nomination her son told me that it brought a smile to her face and she and her husband Hank started to plan for her return to ICW in 2020, but that trip was not to be. Instead of her presence, this article stands as a poor substitute. Her tales of the early use of complement work in the US were clearly lively and sometimes continuous. It was my privilege to hear Dr. Giclas tell the tails but I cannot relate her stories with the candor and humor we all know so well.

When I think of how Dr. Giclas's impacted complement starting with her pivotal research (we would be well served to revisit her work in light of today's pandemic) to her early understanding of the importance of quality, accurate complement testing in the diagnosis of human diseases (something that has gained traction only in recent year), I am impressed anew with her pioneering spirit. Dr. Giclas started her academic career at the University of Arizona in 1956 where she studied physics and mathematics. Before finishing that degree Dr. Giclas made the decision to put her family first and stepped away from her schooling for 10 years to raise her two sons. When they started school, Dr. Giclas herself returned to her studies, finishing her BS in Biology with high honors at New Mexico Institute of Mining and Technology. From there Dr. Giclas moved to Tucson where she completed her PhD in Molecular Biology at the University of Arizona. It was during her graduate studies that Dr. Giclas started her work in complement immunobiology. Then she was off to the Scripps Clinic and Research Foundation where she worked from 1975 to 1977 in one of the nation's more dynamic and active complement research programs. In 1977, Dr. Giclas made the move to Colorado to continue her work in complement at what was then known as National Jewish Medical and Research Center, following her mentor Dr. Peter Hansen. It was at National Jewish Health that she built her career. Eventually she and Hank bought a house in the inviting foothills of the Rocky Mountains but in her early years in complement research she demonstrated her tenacity for the field by living in Denver with one son while Hank's work kept him and their other son in New Mexico.

When I look back as Dr. Giclas's publications, I am struck by how much of her early work has bearing on the current pandemic and 'new' questions arising from the advent of complement therapeutics. It reminds me again how deep her 'unpublished' knowledge of the complement system went and how lucky I am to have her as a mentor. Dr. Giclas's PhD work and early publications focused on the activation of complement by subcellular membranes, particularly the membranes of the cardiac mitochondria. She also outlined several mechanisms of activation of complement that are outside our textbook thinking about complement. Specifically, in her early work she helped define an IgG independent activation of complement by monosodium urate crystals, as well as activation of complement by a specific strain of Western Red Cedar. The latter was a help in figuring out why a specific group of loggers and sawmill workers were coming down with asthma. This work was a

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prelude to her important role in complement diagnostics and therapeutics. Dr. Giclas adeptly utilized studies of rabbit complement to broaden our understanding of innate immunology, elucidating the acute phase response of C3 and C5, as well as work on the interaction of complement and plasma kallikrein. But an area of work that was met with derision at the time, but now is most salient to the current pandemic, is Dr. Giclas' work in complement and the lung. In the 1970's and early 1980's her grant applications to NIH to work on the lung and complement were given poor scores. She shared with me that she often received comments like 'there is no complement in the lung so there is no merit to the application'. We know now that that is far from the truth and have seen strong evidence for a role of complement in the dramatic effects of COVID-19 where complement therapeutics show promise. We may all do well to re-read her work elucidating complement and the lung in general, and the role of this complement cascade in the acute respiratory distress syndrome, specifically.

Dr. Giclas was not one to walk away from her belief in the role of complement because some reviewers could not see what she clearly saw. She stayed in the field, using her strong skill set and her aptitude for complement analysis to answer the queries of physicians and patients. At the time complement testing was not at all common in the US and where it was available it was highly limited. Dr. Giclas soon recognized there were more patients suffering from undiagnosed complement disorders than had been previously recognized, so she put her expertise to work to develop reliable diagnostic testing. She soon proved not only was she a pioneer in complement but also was a pioneer in clinical immunology testing. She quickly built her reputation for a deep understanding of the clinical effects of complement activation, authoring numerous chapters and books on complement testing. This too was pioneering work, as we now see complement testing in some form in almost all large clinical testing laboratories. Dr. Giclas joined with her colleagues from across the globe to start the efforts that are now the ICS Committee for the Standardization and Quality Assessment of Complement Measurements.

This increase in testing is driven by not only the increase in awareness of the role of complement in human disease, but also by the advent of biologic-based, novel new drugs, an area again where Dr. Giclas was a pioneer. In the 1990's Dr. Giclas was part of the team who determined that the new class of therapeutics based on small interfering RNA could dramatically activate complement through the alternative pathway after unexplained and dramatic effects were seen in pre-clinical trials. This launched her work in Investigational New Drug development under the US FDA drug development requirements. This preceded the advent of the first complement specific drug, but set up the framework for this regulated work and added to her deep understanding of the potential clinical consequences of unwanted complement activation.

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While I could not do justice to her stories, I hope I was able to share enough of her work to paint the picture of Dr. Patricia C. Giclas as a tenacious, complementologist who didn't take 'No' for an answer. She paved her own path, balancing her career and her family in ways that would have been too hard for some. She moved research, diagnostics and therapeutics forward for the benefit of so many.

Ashley Fraser-Abel, Ph.D.

Patricia C. Giclas, Ph.D.

Winner: Pioneering Women in Complement

Pioneering Women in Complement Research Award

In Memoriam

Jarmila Janatova, Ph.D.

January 9, 1939 – July 13, 2020

After a prolonged illness, on July 13, 2020 our dear friend and colleague Dr. Jarmila Janatova died at her home in Salt Lake City, UT. With her passing, the complement field has lost an extraordinary biochemist, one who played a very prominent role in the discovery of the thioester bond in C3 and C4, the entity at the heart of their ability to covalently attach to foreign targets. Shortly before her death, the International Complement Society recognized Jarmila's vital contribution to this important milestone in our field through her selection for one of the three inaugural Pioneering Women in Complement Research awards.

Although hailing from the relatively small town of Pisek, Czechoslovakia, Jarmila received all of her formal education in the culturally rich capital city, Prague. She received an M.Sc. in Chemistry from Charles University in 1961 and a Ph.D. in Biochemistry from the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences for work on human serum albumin. From 1966-1967 Jarmila was a postdoctoral research associate working on bovine serum albumin with M.J. Hunter at the University of Michigan, Ann Arbor, including the characterization of free sulfhydryl group presence in various forms of albumin. From 1967 to 1973 while in England due to her husband's job, Jarmila took a break from her lab research career to raise her children Petr and Hana, but still found time to write a major review on the heterogeneity of serum albumin. Jarmila and her family then returned to the United States and she began her long association with the University of Utah in Salt Lake City. Initially, there were a couple of fairly short term postdoctoral research associate positions, first in the lab of W.R. Gray working on tropoelastin (1973-1975), then in the lab of J.D. Andrade working on albumin and biomaterial protein adsorptions (1976-1977), separated by another year in England in between. In the fall of 1977 Jarmila joined the lab group of Dr. James W. Prahl who, together with Dr. Brian F. Tack, had been working for a number of years on purification procedures and other biochemical characterizations of complement proteins C3 and C4 when they were both in the Washington, D.C. area. Their collaboration continued after Dr. Prahl's arrival in Utah in 1975. A major question of the time in the complement field related to the mechanism of the so-called labile binding site through which a small portion of nascently-activated C3b or C4b could attach the protein to target surfaces, while the rest of the material, which did not immediately find a target, in each case became inactive in the fluid phase. It was towards elucidation of this question that Jarmila joined in on the Prahl lab effort, an effort that ultimately led to the inferential proposal, and then more definitive proof, of the existence of an internal thioester bond in C3 and C4. The key events described below in the discovery of the thioester (or thiol ester, using Jarmila's preferred nomenclature) are largely gleaned from a first person account that Jarmila wrote in a 1983 New York Academy of Sciences review on the topic.

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Just prior to Jarmila Janatova's arrival in the Prahl lab, Alex Law and Paul Levine published their paradigm-shifting PNAS paper suggesting that a covalent ester bond was formed between nascently-activated C3b and the C3 convertase-bearing target surface, but the mechanism was unknown. The Prahl lab group was aware of some quite old literature showing that nucleophilic reagents such as hydroxylamine and hydrazine, as well as chaotropes and low concentrations of denaturants could render C3 and C4 "hemolytically inactive", which they understood to mean that the treated molecules could no longer deposit onto convertase-bearing red cells. As part of a systematic effort to determine what biochemical changes in C3 were brought about by these treatments, the group decided to examine whether there was a change in free sulfhydryl content. This is where Jarmila's vast experience in quantifying the presence of free sulfydryl groups in serum albumin isoforms surely came into play. Jarmila and her colleagues found that compared to native C3, which had no accessible sulfhydryl groups, all of the above treatments resulted in the release of one sulfhydryl group per molecule of C3, as did enzymatic conversion of C3 to C3b. When ^{14}C-iodoacetamide was used to radioalkylate the free SH group, the label was localized to the elastase-generated C3d fragment and it was confirmed to label a cysteine side chain SH. Upon extensive trypsin digestion of hydroxylamine-treated C3, chaotrope-inactivated C3, and enzymatically-produced C3b, all of which were radioalkylated, the label localized in each case to a single tryptic peptide, but whereas in a two dimensional peptide mapping experiment the migration of the peptide from C3b and the chaotrope-treated C3 were identical, that from the hydroxylamine-treated C3 was slightly different, as one would expect if the hydroxylamine nucleophile covalently modified a reactive carbonyl in C3. In a Biochemistry paper in 1980 in which Jarmila Janatova was the first author, the above-described biochemical insights allowed the group to be the first to propose the existence of an internal thiol ester bond in C3 and that this entity mediated the transesterification of nascently-activated C3b to target hydroxyl groups. The very sad part of the story is that just as the last of these ground-breaking experiments were being completed in late June 1979, Dr. James Prahl, died on a mountaineering excursion. Jarmila continued the long distance collaboration with Brian Tack, now in Boston, to solidify their proposal of an internal thioester in C3. Using ^{14}C-methylamine as the nitrogen nucleophile, and through some very clever solid phase thiol chemistry, it was possible to isolate a tryptic peptide containing the free thiol generated by the 14C-methylamine incorporation into C3 and which could then be radioalkylated with 3H-iodoacetic acid. Then through Edman sequencing, the location and residue identities of the labeled amino acids could be determined. This led to the identification of the sequence within the double labeled peptide as Cys*-Gly-Glu-Glx*, where Cys* was ^{3}H-carboxymethycycteine and Glx* was ^{14}C-γ-glutamylmethylamide. The close apposition of the liberated sufhydryl and the nucleophile-reactive carbonyl group strongly suggesting that a thioester formed between the thiol of the cysteine and the carbonyl side chain of the glutamyl residue 3 amino acids C-terminal, thus forming a 15-member thiolactone ring entity. The Glx was subsequently identified as Gln when the C3 cDNA sequence became available. In follow-up studies, the Janatova/Tack collaboration went on to provide evidence for the presence of the thioester bond in C4, but not C5.

Pioneering Women in Complement Research Award

In 1981 Jarmila was formally appointed as Research Assistant Professor in the Department of Pathology, at the University of Utah, Salt Lake City. She rose to the Associate rank in 1985 and the Adjunct Professor rank in 2004. In 1986 Dr. Janatova became an Academic Member of the Centre for Biopolymers at Interfaces and then she switched her Departmental affiliation to the Department of Bioengineering, University of Utah. With these changes in her appointment, Jarmila's work also transitioned to having a greater focus on biocompatibility issues of complement with medical biopolymers, as well as studies on the biochemistry of tear proteins and their inhibitors. Together with her graduate students and collaborators, Jarmila had many publications on these topics, as well as others involving methods development of biosensors, but every now and then, Jarmila would still have publications true to her more "traditional" passion of complement protein structure-function relationships. Another noteworthy contribution that Jarmila Janatova made to the complement field was in her role as Secretary on the organizing committee for the very successful ICW XVIII held at the Snowbird Resort, near Salt Lake City, Utah in July 2000. Jarmila Janatova retired from active service at the University of Utah in 2011, retaining the title of Adjunct Professor Emerita in the Department of Bioengineering.

I (DEI) will always remember my first meeting with Jarmila. The date was the morning of July 9, 1979 standing in front of our side-by-side poster boards at the International Congress of Biochemistry meeting in Toronto. Jarmila's poster on the presence of a single sulfhydryl group in nucleophile-, chaotrope-, or denaturant-treated C3 and C4 had most of the elements of the studies that she and coworkers subsequently published in their landmark papers starting in September 1980. However, the Toronto meeting was a mere week after the tragic death of Dr. James Prahl, and although Jarmila was over the moon with enthusiasm and satisfaction about her scientific results, she was at the same time distressed not only about the loss of her dear friend, colleague and mentor, but also about what the loss of Dr. Prahl, as her scientific advocate, might mean for her career path in Salt Lake City. Because of our overlapping interests in C3 and C4, as well as our biochemistry roots, Jarmila and I bonded very well and we made a habit of sharing at least one meal when we saw each other at conferences in subsequent years. One of these occasions occurred quite early on in our friendship and was at a FASEB meeting in Atlanta, GA. When arranging for a time and place, Jarmila said that dinner would have to be on the early side because she had two tickets to an event that evening and would I like to come. I of course accepted thinking that the tickets might perhaps be for some sporting event that evening. But alas, Jarmila had probably decided that it would be good for me to get some "culturing", and so she took me to a performance by the Atlanta Symphony Orchestra. I very much enjoyed the performance, but I enjoyed even more watching Jarmila's enthusiasm about the musical pieces and the quality of their performances. Characteristic of the loud speaking voice with which Jarmila would deliver her complement talks, I can still hear her shouts of BRAVO and BRAVA at the conclusion of the performance. I have very fond memories of our friendship and the many laughs we shared together. I shall very much miss not having the opportunity to share a laugh with her again.

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I (AJT) remember Jarmila for many things – her loud laugh making light often of her own disappointment, her love and devotion to her children throughout all stages of their lives, and as an example of how hard it was to be an independent woman in science at that time and particularly without sufficient professional support networks. Many women of that era (who had to make a choice) chose a different path. Jarmila chose to continue to struggle. As further evidence of her love of music and outdoor sports, on a visit to University of Utah, I took an extra day to visit with her. We went skiing all day and then to the symphony that night. Great day, great evening, great conversations – great friend.

Jarmila was much loved and highly respected by the complement community and she will be greatly missed. Jarmila is survived by her son Petr Janata (neuroscientist), daughter Hana Janatova (musician), brother Josef Tichy, and grandchildren Oliver and Sam Janata. On behalf of all complementologists, we extend our heartfelt condolences to Jarmila's family.

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Jarmila Janatova, Ph.D.

Winner: Pioneering Women in Complement

Complement Research at Nijmegen, The Netherlands

The groups of Prof Dr Bert van den Heuvel, Dr Elena Volokhina and Dr Nicole van de Kar

Since 1990 our research is focused to unravel the pathophysiology in renal disorders, in particular hemolytic uremic syndrome (HUS) and C3 glomerulopathy (C3G), with our ultimate goal to find the best treatment for HUS- and C3G patients. In the early years we started studying the effect of Shiga toxin on various human cells as part of examining the pathogenesis of Shiga toxin producing *E.coli* HUS (STEC-HUS). Our complement journey began with a family with three members having non-STEC-HUS in the mid-nineties. At that time the genetics of complement regulators became important in the pathogenesis of this so-called atypical HUS (aHUS).

The scope of our complement research is to examine the role of pathological complement activation on the cell surface in renal disease. As models we use human-derived glomerular cells, patient-derived blood outgrowth endothelial cells and, more recently, kidney organoids. Furthermore, we are performing in-depth analyses of the pathogenic roles of genetic aberrations and autoantibodies in aHUS and C3G. Currently, our group is leading the CUREiHUS-study, a Dutch national observational study on restrictive eculizumab treatment of aHUS patients. In our lab we are measuring serum eculizumab levels, C5-eculizumab complexes and eculizumab inhibiting capacity in a national cohort of aHUS patients. We aim for continuous growth in quality and spectrum of complement diagnostics to facilitate the clinicians in the best treatment of complement-mediated diseases in the Netherlands. Together with team of pediatric and adult nephrologists in our hospital, we are recognized as national HUS/C3G expertise center and are a part of the European Rare Kidney Disease Reference Network (ERKnet).

Nowadays we are a national reference laboratory for complement diagnostics, in particular in HUS and C3G on both protein and DNA levels. The full complement diagnostic packages for these kidney diseases and other complement disorders such as age-related macular degeneration are available and include gene screening, CFH/CFHRs MLPA, whole exome sequencing, as well as all kinds of complement protein analyses (e.g. Factor H, Factor I, Factor D, Factor B, properdin), functional complement assays, complement activation markers (e.g. sC5b-9, C3bBbP , C3bc, C3d, C4), C3NeF, C4NeF and autoantibodies against Factor H, Factor I and Factor B.

We always welcome stimulating collaborations with multidisciplinary teams at local, national and international levels and believe that this is the way to move forward in this extraordinary exciting field of complement!

Contact: Prof Dr Bert van den Heuvel, Dr Elena Volokhina, Laboratory unit complement-mediated disorders or Dr Nicole van de Kar, Dept. of Pediatric Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands.
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Complement Research at Tübingen, Germany

The group of Professor Simon Clark

In October 2019, after twelve years in Manchester studying the role of complement regulation in ocular diseases such as age-related macular degeneration (AMD), Simon Clark was appointed the Helmut Ecker Endowed Professor of AMD at the Eberhard Karls University of Tübingen, Germany. While retaining an honorary Professorship at the University of Manchester, the Clark lab has been slowly transferring from the UK to their new facilities in Germany. Simon is joining forces with Prof. Marius Ueffing, Director of the Institute for Ophthalmic Research and a leading expert in systems biology and ocular genetics, to elucidate the molecular mechanisms underlying AMD. They are particularly interested in better defining the altered biochemical pathways resulting from the two predominant genetic risk loci for AMD (on Chromosomes 1 and 10) and whether these independent initiators may eventually converge around a shared antagonistic pathway in late-stage disease.

Given the Institute's integration within the Tübingen Eye Hospital's clinics, researchers and clinicians work closely together to develop innovative new experimental models. These include human retinal co-cultures with iPSC-derived RPE cells from AMD patients grown on human Bruch's membrane, effectively re-creating a retina in a laboratory environment. Delivery of novel therapeutic concepts into the clinic is driven through the Department of Ophthalmology's own clinical trials team, which has extensive experience in running trials for a range of ocular indications. Additionally, with the retirement of Simon's long-term collaborator and colleague, Prof. Paul Bishop, Simon is the current custodian of the Manchester Eye Tissue Repository, housing >1200 donors worth of phenotyped and genotyped human eye tissue samples. This facility will also be relocating to Tübingen, where it will be supplemented with new collections of human donor eyes and blood collections from patients from the Tübingen clinic.

Following our recent discovery around the genetically-driven role of the complement protein factor H-related protein 4 (FHR-4) in AMD pathogenesis (Cipriani et al. (2020) Nature Commun) the Clark lab is expanding its research around the FHR proteins. By using unique reagents capable of distinguishing all of the FHR family members in biological samples, we are taking advantage of access to well-characterised clinical samples to understand how these proteins modify complement activation in human tissues. Additionally, members of the Clark lab have recently identified a number of non-canonical roles of fluid-phase complement regulators that appear to modify the homeostasis of specific cells found within the human retina.

Alongside the team remaining in Manchester, we have begun recruiting new members to lead the research in Europe. Ms Klaudija Masarini, an established technician with experience in ocular genetics and animal models, has led the set-up of the Clark lab facilities in Tübingen and continues to support our growing team. The lab will soon be joined by Dr. Sonika Rathi, currently at University of Pennsylvania USA, who will be using iPSC-RPE cells from patients with specific risk genotypes for AMD. These samples in co-culture models will investigate the effect of genetic risk variants on neighbouring cells and tissues with respect to complement turnover, activation and tissue homeostasis.

We have been privileged to have collaborated with numerous labs around the world over the years and wish to continue extending a welcoming environment for any visiting students and researchers, who would like opportunities to learn more about complement biology in the eye. Indeed, the Clark lab in Germany remains actively recruiting new team members, and enquires are welcomed.

Complement Research at Tübingen, Germany

The group of Professor Simon Clark

Prof. Simon J. Clark

Prof. Marius Ueffing

Ms. Klaudija Masarini

Dr. Sonika Rathi

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Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition

Jia Yu , Xuan Yuan, Hang Chen, Shruti Chaturvedi, Evan M Braunstein, Robert A Brodsky

Blood; 2020 Sep 2; blood.2020008248.

Infections with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are currently a major threat to the human population worldwide. In search for safe and efficient therapies and vaccines it is important to understand how SARS-CoV-2 causes infections, whether complement is involved, and if complement inhibition is in an option to control infection and to minimize tissue damage. In this study, the group of Robert A Brodsky in Baltimore followed the mechanisms of endothelial damage induced by SARS-CoV-2 spike protein subunits 1 and 2, and N protein. They were interested to see which branch of the complement system is activated, and which effector pathway of the cascade may drive pathology initially in lung tissue and then in the whole body. Addressing these issues allows for a better understanding of the role of complement, and can further suggest which complement inhibitors might be effective to combat the infection and/or the disease symptoms. The study analyzed how the SARS-CoV-2 surface proteins spike 1 and spike 2, as well as protein N activate complement and if the proteins induce endothelial cell damage. The researchers followed C3c, C4d and C5b-9 deposition on the surface of genetically modified endothelial cells (TF1PIGAnul)s and showed that spike 1, 2 proteins, but not the N protein, activate predominantly complement via the alternative pathway and that the proteins induce complement damage of endothelial cells. In addition, complement activation was followed in fluid phase by determining Bb generation in plasma. Both viral proteins substantially enhanced Bb generation. The authors bring up an interesting hypothesis. They show that both spike proteins bind to heparin and thus compete with Factor H for cell surface binding. Thereby the viral proteins reduce the protective regulation by this Factor on the cell surface. Evaluating three complement inhibitors, the Factor D inhibitor ACD 14951 (Achillion) and C5 Inhibitor (Alexion), as well as Factor H, the authors demonstrate that complement inhibition reduces cell damage and protects endothelial cells from SARS-CoV-2 induced damage. In conclusion, the study demonstrates that SARS-CoV-2 spike proteins strongly activate complement on the surface of endothelial cells and by competing off Factor H convert non-activator cell surfaces to activator surfaces, which exacerbates the damage by the virus. These data together with other recent excellent reviews and interesting research papers link the complement system with the infection process induced by SARS-CoV-2, and more importantly give complement inhibitors a promising future to control the deleterious effects induced by this virus.

Complement genes contribute sex-biased vulnerability in diverse disorders

Nolan Kamitaki, Aswin Sekar, Robert E. Handsaker, Heather de Rivera, Katherine Tooley, David L. Morris, Kimberly E. Taylor, Christopher W. Whelan, Philip Tombleson, Loes M. Olde Loohuis, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Michael Boehnke, Robert P. Kimberly, Kenneth M. Kaufman, John B. Harley, Carl D. Langefeld, Christine E. Seidman, Michele T. Pato, Carlos N. Pato, Roel A. Ophoff, Robert R. Graham, Lindsey A. Criswell, Timothy J. Vyse & Steven A. McCarroll

***Nature*; 2020; 582:577–581**

Complement proteins are important for human health. It is known that gene variations, as well as mutations can contribute to, and drive pathology in several human disorders. Allelic variations and gene polymorphisms of complement genes are increasingly receiving attention in disease pathologies, and now, have also been linked with the involvement of gender differences in disease. In this study, a consortium of researchers from Harvard, Boston, USA; Kings College in London, UK and several other laboratories demonstrate new important results detailing how complement genes are involved in gender specific diseases. The study shows that the C4 gene, with the two allelic variants, C4A and C4B, contributes to three human disorders and to sex bias for disease susceptibility. The disorders include the two autoimmune diseases Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome, and schizophrenia. SLE and Sjögren's Syndrome affect nine times more women than men. In contrast, schizophrenia affects men with higher frequencies than women. Furthermore, all the three diseases show a strong genetic association with the major histocompatibility complex (MHC). This multi-author study consortium demonstrates that specific C4 genotypes, which are also linked to the MHC locus and which was already known to be associated with schizophrenia, have a 7-fold increased risk for SLE and 16-fold risk in Sjögren's Syndrome. Among individuals with the common C4 genotypes, C4A had a stronger protecting effect, than C4B in both SLE and Sjögren's Syndrome. Interestingly, the alleles that reduce risk in SLE and Sjögren's Syndrome, show a greater risk for schizophrenia. In addition, the C4 alleles have a stronger effect in men as compared to women. The common risk combinations of C4A and C4B, generated a 14-fold increased risk for SLE and a 31-fold risk in men for Sjögren's Syndrome, and results in a 1.7 fold increase in schizophrenia. By contrast, the risk ratios in women were 6, 15 and 1.26-fold variants. These effects influenced protein levels of both C4 variants and also of C3, when evaluated in plasma and in cerebrospinal fluid. Again, C4 protein levels were higher in men compared to women. These examples in three diseases demonstrate that allelic combinations of C4 genes are relevant in human disorders. The new data highlight the central role of the complement system, in its various combinations and polymorphism of single genes, for disease severity and progression of human disorders. Furthermore, the data demonstrate that sex differences exist in the composition of plasma complement components can be different. Such variations of complement components in men and in women may be relevant for an individualized therapy approach.

ICS C³ Symposium: Complement, Clotting & COVID-19

Wednesday, 28 October 2020 - ZOOM - 09:00-12:00 ET (15:00-18:00 CET)

Welcome & Closing Remarks

Peter Garred, MD, PhD
President ICS

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Claudia Kemper PhD	Steven Holland MD	Daniel Ricklin PhD	Ben Afzali MD, PhD	Tom Erik Mollnes MD, PhD	Marina Noris PhD	Éric Vivier DMV, PhD
						
Introduction & Moderator	The NIH-led Efforts to Combat SARS-CoV2	Current Status of Complement and COVID-19	Local Complement Hyperactivation in the Lung Induced by SARS-CoV2	Systemic Complement Activation: Respiratory Failure in COVID-19 Patients	Complement, COVID-19 and Thrombosis	COVID-19 and the C5a Axis

Registration Opens 02 October at: www.complement.org

Conference Postponed to: June 17-22, 2021

13th International Conference on Complement Therapeutics

The field of complement-targeted drug discovery has experienced a profound transformation during the past decade. With the first complement-specific drugs on the market, clinical experience is gained and novel indications are being explored. At the same time, efforts in both academic and pharmaceutical research have produced new innovative therapeutic concepts and drug leads that interfere at different levels of the complement cascade; many of these candidates are currently undergoing clinical evaluation. Finally, genetic and molecular studies continue to reveal contributions of complement in both orphan and highly prevalent diseases. Apart from offering new hope for patients suffering from such diseases, the study of complement pathways, mutations, and deficiencies also teaches us important lessons about the role of complement in health and disease and allows us to refine our models and tools for applied and basic research. This conference aims to bring together academic and industry scientists and clinical development experts who are focused on contemporary and emerging aspects of complement-mediated disease pathogenesis and the development of therapeutics that modulate this system in a beneficial manner.

Topics discussed during the conference include: Molecular mechanisms and targets in complement-related diseases; Novel inhibitors & pipeline compounds; Hematological disorders; Organ & cell transplantation, I/R injury and chronic rejection; Kidney diseases; Neurological & ocular diseases; Acute and chronic inflammatory disorders; Infectious diseases & sepsis; Cancer; Informative complement biomarkers in therapeutic development; Novel and unexpected indications.

Organizing Committee:
John Lambris, PhD
Dimitrios Mastellos, PhD
Daniel Ricklin, PhD
Antonio Risitano, MD
Lubka Roumenina, MD

17th - 22nd June 2021
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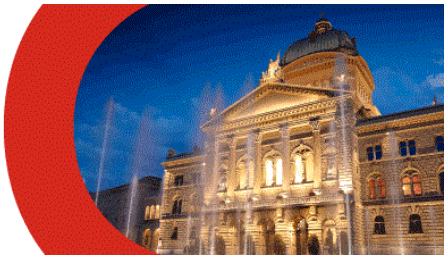

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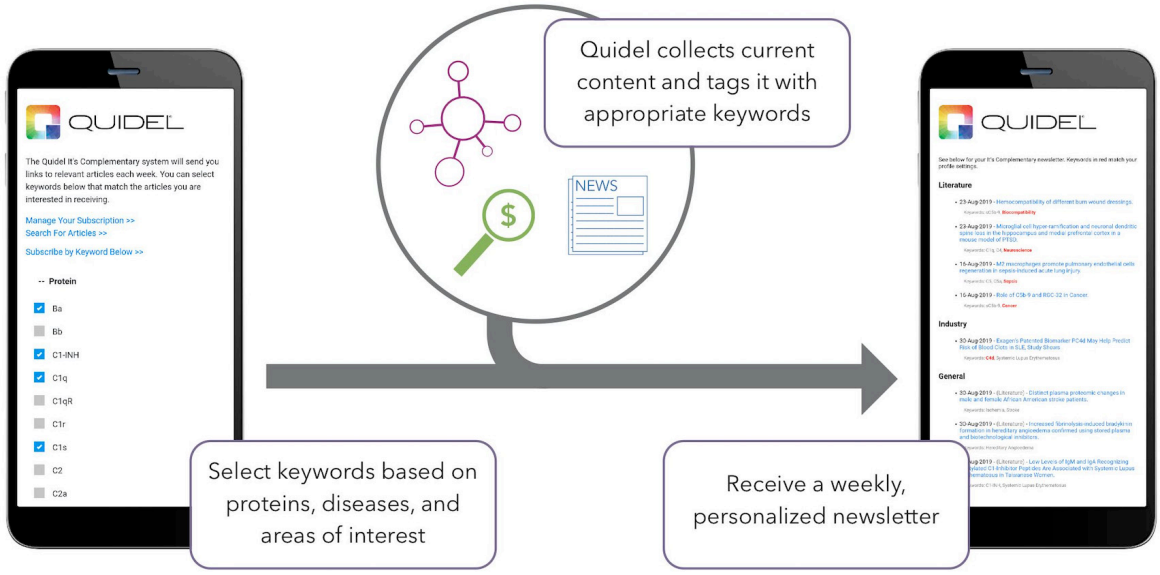

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